ANNUAL REVIEW OF PHYSIOLOGY

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PREFACE

The *Annual Review of Physiology* owes a great debt of gratitude to the distinguished group of men, all now elder statesmen of physiology, by whose efforts it was organized and launched on its career of service. Among these none was more devoted and helpful than Dr. Frank C. Mann, who served on the Editorial Committee from its beginning until 1951, and was Chairman during the last four of these years. We are therefore particularly happy to have him as the author of the Prefatory Chapter of this volume, and count as well spent the editorial effort required to overcome his modest resistance to set down this account of his personal development and convictions. We are confident that his many devoted friends will find in them something of the warm simplicity and kindliness that they have known in personal relations with him, and that those who did not have this privilege will profit by his reflections on the problems of those physiologically inclined.

A number of changes have occurred this year in the Editorial Committee. Dr. W. F. Hamilton has retired as Chairman and has been succeeded by Dr. J. P. Baumberger. We have also lost the valued service of Dr. M. B. Visscher. The vacancies thus created have been filled by the appointment of Dr. H. W. Magoun and Dr. G. K. Moe.

Three years ago we began the practice of including in each volume a chapter on some major aspect of comparative physiology. Reviews on muscle, on invertebrate endocrines and on nervous systems and sense organs have appeared in this series, it being planned that each topic would again be reviewed after an interval of about five years. The favorable reaction to these chapters plus the pressure brought on us by workers active in the comparative field have encouraged us to further efforts in this direction. Accordingly we offer in this volume two such chapters, one on respiration by Dr. E. Zeuthen and one on nutrition and digestion by Dr. H. J. Vonk. We believe that this course is justified, not only by inherent interest of studies made on a wide variety of animal species, but also by many instances in which such studies, taking advantage of special features afforded by lower forms, have made possible advances in the understanding of processes common to all forms of animal life.

J.P.B.	V.E.H.
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page 371, line 20: for 0.116°C. read 0.18°C. (erroneously entered in Volume 11, page viii, under Errata as page 1 instead of 371).

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FRANK C. MANN, M.D., LL.D., D.Sc.

TO THE PHYSIOLOGICALLY INCLINED

By Frank C. Mann

Emeritus Member, Division of Experimental Medicine, Mayo Foundation and Mayo Clinic, Rochester, Minnesota

When the editor of the *Annual Review of Physiology* first presented his suggestion for a special prefatory chapter with its objectives to the Editorial Committee of the *Annual Review*, I supported it with enthusiasm. The excellent chapters written by DuBois (1), Wiggers (2), Gerard (3) and Loewi (4) served to maintain this enthusiasm. When I was honored by the invitation to write the chapter for volume 17, I suddenly lost all enthusiasm for both the chapter and its objectives, not only because I dislike to write, but also because I realized my inadequacy for the task. I accepted the invitation only because I believed I had a responsibility to the editor, since I was chairman of the Editorial Committee at the time the prefatory chapter was initiated. I shall again be enthusiastic about the chapter for the next volume.

In the preparation of this chapter I have, to a considerable extent, written three articles. At first I tried a historical theme, but soon found that the product was but a weak, diluted imitation of the superior chapters of DuBois and Wiggers. Next, I made an attempt to write philosophically, but the remembered remnants of my university courses in philosophy that had not been filtered out by the passing years did not appear to apply to physiology. I knew I could not write knowingly about a profound subject, as Gerard did, because I have not as yet mastered all that is contained in his excellent chapter. I finally realized that there are many physiologists who could write more authoritatively regarding the history and philosophy of physiology than I; that if I were to contribute anything that might be of value in accordance with the stated objectives for the chapter, anything that could not be written much better by other physiologists, the subject must necessarily deal with phases of physiology, even though of minor importance, that related to an undesired extent to myself. Therefore, I have done boldly what Loewi did with effective timidity: written with an embarrassingly large and frequent I.

While this article is partially autobiographical, I disclaim any personal desire to have it thus. It would be of no profit for a scientist, whom the stealthily passing years had pushed out of his laboratory, to attempt to inflate the value of his past work beyond original worth. Rather, it is the desire that the autobiographical part will but serve as a simple story in which failures, mistakes, and modest successes will emphasize by inference the many factors responsible for the ever-changing and rapidly-expanding science of physiology, and above all the hope that the story will indicate the importance of chance, the unpredictable, in altering the pre-planned course. The over-all objective is the hope that the story may prove of value to the physiologically inclined, the student on the threshold of deciding whether or not to embark

on further training in physiology for either a career in that field or as a physiologic participant in some related profession.

By the time I was six years of age I had determined to be a doctor, and with my broken-bladed pocketknife I attempted to dissect, before burying them, various parts of the fowls and animals that had died on the farm. In addition, my father taught me to assist him with the necessary obstetrical duties required by our registered sheep, and with other tasks having to do with the farm animals. When I had completed my sophomore year in medicine at Indiana University (1909), I realized that I would not be satisfied without more knowledge of physiology. The two years I spent in the department of physiology, assisting in the laboratory work, taking courses, and trying to do research, were not a sacrifice of time. My chief, W. J. Moenkhaus, was a very kindly man to students and an unsurpassable teacher. From him I learned to appreciate some of the problems of the student and to dislike the fellow who elbows. He was rather unambitious, although he made some valuable investigations in genetics and was probably the first investigator to use the banana fly for such studies.

My problem in physiology, of necessity worked on mainly at night and week ends, was to attempt to repeat the work of Edkins (5) on gastric secretin. All the experiments, because of lack of animal quarters, were done with the animals under the influence of anesthesia. A suction method for securing repeated samples of gastric secretion was developed. The pyloric mucosal extract was made as described by Edkins. I not only was able to make the extract from the mucosa of the common laboratory and domestic animals but, since the winter quarters of a circus were near by, I was able to obtain many other species of animals, such as the camel, snake, parrot and other birds.

In each of the more than a dozen species obtained, an extract was prepared, which, upon intravenous injection, caused a marked decrease in blood pressure and which in the anesthetized cat, rarely in the anesthetized dog, was associated with a secretion of acid gastric juice. Before the investigation was completed, it became evident that much work on fractionation would be required before it could be proved that a specific gastric secretin was contained in the crude extract. Since facilities for such work were not available, the research was abandoned.

My second venture in research was with Dr. D. E. Jackson, who has great skill in making fine physiologic apparatus, an unbelievable memory, and immeasurable energy. Dr. Jackson had the idea that the emanations from uranium might alter hemoglobin. Spectrograms of the blood of dogs, taken at various periods after injection of a salt of uranium, were made. The physics department of the university was fortunate in possessing an original Remsen diffraction grating which, with many cautions and much misgiving, was loaned to us for night use only. One of my jobs was to control the carbon points of the lamp for proper lighting. This required looking directly at the bright light. We were ignorant of the danger to the eyes of such a procedure

and did not use protective glasses. If I ever go blind, I will claim the occurrence a sacrifice to science. The results of the research eventually were published, and Dr. Jackson honored me by recognition as an assistant, which was the first appearance of my name in scientific print (6).

At the end of my junior year in medicine I knew I was going to be a surgeon. This decision was to a great extent based on admiration of my surgical chief, W. D. Gatch, a stimulating, original, and forceful teacher, and his surgical skill. At the end of my senior year in medicine an excellent training in surgery was assured me. I was to be the surgical assistant to my chief in an almost-completed new hospital of the university, with the opportunity of developing an experimental laboratory course for senior students, a course which was to include surgery, anesthesia, and applied physiology. In addition, research was planned, as time permitted.

The first surgical research laboratory in which I worked was located in an abandoned anatomical dissecting room. The equipment and personnel consisted of a few dollars' worth of instruments, some discarded dissecting tables, some homemade cages and a young, versatile Negro who served as animal caretaker, diener, anesthetist, and surgical assistant, During our senior year, a fellow classsmate and I, under the direction of Dr. Gatch, completed a simple investigation. Dr. Gatch, by magnifying the importance of this investigation, was able to convince the custodian of the university exchequer that our work justified a trip, with traveling expenses paid, to the annual meeting of the American Medical Association which was to be held in Minneapolis (1913). In addition, our professor of medicine, Dr. Wynn, who was the founder of the scientific exhibits of the American Medical Association, offered us a per diem compensation to take charge of the scientific exhibits.

The scientific exhibits were housed in two rooms of the department of pathology at the University of Minnesota Medical School. There were eight main exhibits, but only four will be mentioned. The most outstanding exhibit was by Dr. Smith, of the Bureau of Plant Industry of the U. S. Department of Argiculture, and consisted of bacterial studies on crown gall with implications regarding its possible relationship to cancer in the human being. The largest exhibit, which was from the Mayo Clinic, was composed of an unbelievably large number of poorly-arranged glass jars containing thyroid glands removed at operation. The specimens had been selected mainly on the basis of size, and therefore probably were of the colloid type. Dr. W. M. Boothby, then anesthetist to Dr. Harvey Cushing, had an exhibit dealing with the partial vapor tension of ether required for various states of anesthesia. Our exhibit illustrated the results of an experimental investigation on the effect of the Trendelenburg position on the circulation (7).

At the end of the meeting we spent one day at the Mayo Clinic. The surgical clinics came up to all my expectations and greatly increased my desire to become a surgeon. Yet in the afternoon I left Dr. Gatch to swelter in the operating room while I visited the first experimental laboratory established

by the institution, and listened with growing interest to the description of the plans for the new experimental laboratory that was to be opened the following spring.

When we arrived back at the medical school I learned to my dismay that construction of the new hospital, which was to have been finished in July had been held up because of a jurisdictional strike. The union that had charge of the outside work and the union that had charge of the inside work had become involved in an argument regarding the laying of the tile in the little foyer, and all work on the building was suspended. At first I utilized my time in the completion of my thesis for the degree of master of arts. The research was an experimental study of surgical shock which resulted in my first publication as a sole author (8). I also assisted Dr. Gatch in some of his operations and began a study of intrathoracic pressure in animals and patients, using a crude water manometer for measurement.

When school opened in the fall I initiated the long-contemplated experimental course for the senior students. However, as the school year progressed and work on the hospital remained at a standstill, I became restless, and Dr. Gatch generously offered to obtain another place for me to secure training in surgery. He wrote Dr. L. B. Wilson of the Mayo Clinic, among others. Dr. Wilson replied that a fellowship in surgery would be available in a few months, but that a personal interview was required. I immediately made a second visit to the Mayo Clinic, taking along my thesis on surgical shock. Before I left Rochester I had the promise of the fellowship. During this visit I had the privilege of viewing the new laboratory for experimental surgery and pathology, which was later to become the experimental laboratory of the Mayo Foundation of the University of Minnesota, and expressed the desire that some time during my fellowship I be permitted to work in the laboratory.

When I returned to the medical school I found a telegram from Dr. Wilson awaiting me. In it he offered me the position of chief of the Laboratory of Experimental Surgery and Pathology of the Mayo Clinic, with a stipend that looked big to me then, but which currently would be little more than the monthly payments on an automobile. I immediately accepted. This opportunity was very timely, because it not only afforded me the chance to do research but also permitted me to take a bride.

I began work in my new laboratory on April 10, 1914. My intention was to spend a few years in research, and then again take up training for clinical surgery. I found that my new position greatly exceeded my expectations. Both Dr. William J. Mayo and Dr. Charles H. Mayo made plain by their actions and words that if they considered an individual worthy of being on their research staff, they also considered him capable of deciding upon the research work he would do and what he needed to do it. This broad and generous policy toward my researches was consistently followed. I never had anything I desired for my work denied, or was subjected to any censorship or criticisms in regard to the problems I desired to investigate or the papers I wished to

publish. However, I soon realized that in this institution, which had so generously accepted me on its staff, an experimental investigator had a unique position of responsibility. Not only were his activities more closely intertwined with those of the clinician than was the case in most research laboratories at that time, but the funds for his researches were earned by his clinical colleagues. Every dollar spent in research had to come from the patient through the work of the clinical members of the staff.

I rank my early recognition of my responsibility in regard to the unrestricted spending of the dollars of the patients, earned by the work of others, as one of my most valuable discoveries, because it forced me to formulate in my own mind some simple but satisfactory policies regarding the work of the laboratory. The experience with my first research problem appeared to indicate that the unfinished and abandoned investigation was probably the most important specific cause of waste, in both time of investigator and monies expended, in research. I am still of that opinion. The answer to this problem appeared to depend, to a great extent, upon the preconceived design of the investigation.

I conceived that, in general, the design of any specific problem should be such that any one of three answers should be obtained. These answers should be an unqualified yes or no, or that a definite answer to the problem could not be obtained by the methods available. It was considered unwise to undertake a research until the design of the investigation was perfected to an extent that gave reasonable assurance that one of the three answers would be forthcoming, and every effort was made to continue the investigation until such an end was attained. Of course, this had to be a back-of-the-mind, unprinted policy because, as every investigator knows, ideas often generate an enthusiasm that will not permit delay of the experimental test. History indicates that a sufficient number of discoveries have been made thus to condone this rashness, but in many instances more progress usually would have been made if the enthusiasm had been cooled with constructive thought.

It was also recognized that frequently in the profitable investigation the design of the research is often discarded because of an unexpected discovery, but this occurrence does not negate the value of the original design. I also decided that since research deals with the unknown, any seemingly worthwhile problem would justify its cost provided the investigation was pursued until one of the above-mentioned answers was definitely recognized. Since the support of the laboratory came from patients, it would seem only just that in general the work of the laboratory should point toward the patient, and the clinical environment of the laboratory made it easy to do this.

Of course, the pointing finger often can be quite a distance from the object to be identified, and the above policy did not prevent me from wandering into problems, such as those of hibernation, which appeared at that time to be devoid of clinical interest. While the foregoing policies would appear to mechanize and circumscribe research to some extent, it should not be inferred that the laboratory was to deal only with the so-called practical prob-

lems. The word "practical" too often appeared to me to be used to cloak ignorance or excuse laziness.

At first, part of my work was the supervision of necropsies, of which about 300 were made annually at that time. This work was very valuable in increasing my knowledge of pathology as well as acquainting me with some of the many problems of patients and their relatives. However, since I was not a pathologist and the necropsy work was a hindrance to my progress in research, I relinquished it gladly after about 18 months.

I was very much surprised at the interest shown in the experimental laboratory by many members of the busy clinical staff of the Mayo Clinic, and especially the surgeons. Dr. E. S. Judd visited the laboratory the afternoon of the day of my arrival. He talked over some of the surgical problems relating to the gallbladder, a structure that had been almost ignored by the physiologist, but which was of great interest to the clinicians and surgeons. That visit marked the beginning of an association that was very stimulating and helpful to me and one which continued until Dr. Judd's death. The discussion at this visit also served as a stimulus for a continued series of researches on the gallbladder and biliary tract.

Dr. H. S. Plummer rarely made any suggestions regarding research but would frequently spend considerable time in the discussion of various phases and problems of science, particularly those that were associated with clinical medicine. I often wished I could have a transcript made of the talks he gave me, because they contained much of value. Dr. Plummer was one of the rare individuals who did not publish enough.

Dr. D. C. Balfour not only helped by his interest in the current researches of the laboratory, but also when both a surgeon and director of the Mayo Foundation made the world seem brighter and the difficulties less by his unfailing friendliness and thoughtfulness. In these respects, especially, he reminds me of Dr. Meltzer, whom I shall mention later.

Dr. William J. Mayo frequently sent me a note containing a question in physiology or regarding some research he had read or heard about. Usually, I could answer these notes from memory or after reference to the literature. Sometimes a simple experiment or two were required before I could make a report to him. However, one time he gave me a real stickler. It was during the war, when he was an adviser to the Office of the Surgeon General of the Army. At that time, gangrene in the limbs of the wounded was a serious problem. Someone in Washington suggested that they be treated by intra-arterial injections of iodine incorporated in a substance that would stop in the capillaries. It was further suggested that Dr. Will have the experimental work done in the laboratory of the clinic. He did not think much of the idea, but felt he was not in a position to refuse. After much reading and experimentation I found that granules of certain varieties of pepper, after exposure to iodine, would fulfill the requirements of the suggestion but, of course, the preparation was of no benefit as a therepeutic agent. Dr. Will did one thing that was always a booster to my morale and was particularly helpful when I

was disappointed by failure in my researches. Usually, after reports of research I gave at our staff meetings or after meetings at which I spoke and he was present, he sent me a brief but stimulating note of approval.

Dr. Charles H. Mayo had the most original ideas of anyone I ever knew. In my early days at the clinic it was a rare week in which I did not receive a note, or very occasionally a visit, from him in which a theory concerning something which was of current interest to him was given. Usually, after explaining his theory, he would inquire if it could be proved wrong. If I replied that I could not prove him wrong, he would say that then he could incorporate the theory in his talk. However, his method of presenting, early in his talk, an unproved theory to interest his audience, so that he could later give some good, sound medical advice, proved to be a successful procedure, except to the speaker who followed him on the program, who with chagrin usually found that he was addressing a diminishing audience.

Dr. L. B. Wilson, who was director of laboratories at the Mayo Clinic when I first arrived at the clinic, was very helpful in orienting me in regard to the clinic during my first two years. He was the most versatile man I ever knew. With the establishment of the Mayo Foundation, his work as director occupied much of his time, but did not prevent the giving of his mature judgment in analysis of our researches.

I could mention many other of my colleagues who aided me, had an interest in research, and brought their clinical problems to me for discussion and evaluation in regard to their research merits. However, enough has been written to indicate that I was in an ideal situation for a researcher with the limited amount of training I possessed. Of greatest importance was the realized presence of a spirit of co-operation, of an enviromnent saturated with clinical problems that might be investigated experimentally, and the mutual urge to do more and more for the ever-increasing number of patients.

Shortly after my appointment to the staff of the clinic I was given the opportunity to visit several different laboratories of famous investigators in physiology and biochemistry. I returned from this visit with the realization that the greatest deficiency of our laboratory was myself, but that our laboratory excelled others in one respect, namely, that it was an integral part of a clinic which afforded me the unusual opportunity to work in co-operation with clinicians on some of their many problems which could be designed for experimental investigation. To profit by this advantage, it was essential to attempt to integrate the work of the laboratory as much as feasible with the work of the clinic, to try to maintain the interest of clinicians in experimental research, and to refer problems to the laboratory in the same manner they referred patients from one section to another.

In 1916 I received invitations to give two papers; one at the meeting of the American Medical Association and the other before the American Association of Anesthetists. I arrived early at the meeting hall where the first paper was to be given and was immediately startled to hear my name paged. Rushing toward the information desk, with all sorts of disasters at home in mind,

I was met by a man with outstretched hand who said his name was Meltzer. Of course, I had known of much of the researches of Dr. Meltzer, because no one working on surgical shock, anesthesia, artificial respiration, or many other fields could have failed to know of him. Dr. Meltzer asked questions about my work, and later discussed both of my papers. Thus began a very inspiring, though all too brief, association with one of the great scientists.

It is not unusual and is wholly desirable for a young scientist to hold as his ideal one or more of the outstanding individuals in his chosen field. There have been many physiologists who have been worthy of such a regard, and among them American physiology has had its share. I am mentioning Dr. Meltzer, not because he should be considered the most outstanding, for there are many others who could with equal justice be given great distinction; not because he made a wholly gratuitous effort to help me, because I am also greatly indebted to so many other great American physiologists; but because he is such a striking illustration for the theme of this article. Dr. Meltzer was a sincere idealist, a rugged champion of the experimental method in research, an enthusiastic physiologist, a physician who diligently attempted to use his knowledge of physiology to aid his patients, a teacher of all who had an interest in science. His criticism of scientific work of others was intensely expressed, but usually dealt only with the work and not the author. His attitude toward the timid youth laying his early offerings upon the altar of science was one of friendly encouragement and constructive criticism which left no sting but only a feeling of admiration, stimulation, and hope of emulation. Above all, his advocacy of the application of physiologic science to medical practice generated a feeling of importance and urgency for physiologic research. He was indeed a worthy ideal for a young physiologist who was being saturated with the atmosphere of clinical medicine.

I received the honor of membership in the American Physiological Society in 1916, and gave my first paper before the society at the Minneapolis and Rochester meeting in 1917. I found so much inspiration, pleasure, and value in these meetings that I attended every one for 35 years.

When World War I came, in spite of the fact that I trained regularly in our volunteer group, I found myself a forgotten reserve, tied down to the teaching of surgical technic to army officers, anesthesia to private soldiers, and during spare time, pursuing some investigations on experimental surgical shock. At various times I also substituted as supervisor of necropsies. All that I recall of this period is the development of a belief that there was a need for better teaching of surgery, and I learned that plasma is a fairly good substitute for whole blood in the treatment of experimental surgical shock.

One rainy morning, while glancing through journals, I noted the report of a necropsy in which the pathologist stated that the only hepatic tissue present consisted of small fibrotic remnants. This statement gave rise to the thought that if a human being could live with such a small amount of hepatic tissue, it might be possible for an animal to live without any liver tissue. In spite of the fact that the results of studies on dehepatized geese and frogs did

not support this idea. I decided to try to remove the liver of a dog. It was obvious that the first problem involved in removal of the liver of a mammal concerned the maintenance of the return of blood from the portal vein and vena cava.

My first effort, that of making an Eck fistula and subsequent ligation of the vena cava, was a failure because sufficient collateral circulation was not established to accommodate the combined amount of blood. The second technic tried, that of reversing the ligation, was successful, and the animal was thus ready for the final operation. The first animal from which I removed the liver died on the operating table. The second operation was successful, and when the animal appeared as normal as other animals did after other operations, several hours after removal of the liver, I felt my deduction from the necropsy report might be correct. However, at the sixth hour after completion of the operation, a previously unrecognized group of symptoms developed in the animal, and it died in coma.

After we had observed the same course of events in several dehepatized animals and had studied such things as pulse, respiration, and so forth, it became evident that chemistry was essential for further progress. My colleague, Dr. T. B. Magath, readily agreed to make the necessary chemical determinations. The first consistent finding we observed was a decrease in blood sugar and the development of characteristic symptoms when the blood sugar became quite low. The decrease in blood sugar was not unexpected, because of previous observations. However, the association of the hypoglycemia with the symptoms was unsuspected.

It now became pertinent to determine if the administration of glucose would alter the condition. I well remember the hot afternoon on the last day of August, 1920, when this question was put to test. The animal was a large mongrel bulldog. The concentration of blood sugar decreased in the usual manner, and $5\frac{1}{2}$ hours after removal of the liver the animal was flaccid. An intravenous injection of glucose was begun, but before the syringe was emptied, to our amazement, the animal suddenly arose and jumped off the table. Within an hour the value for blood sugar had again decreased, the characteristic symptoms developed, and the injection of glucose brought resuscitation. This was repeated many times, with similar results, and the animal lived many hours.

This rather dramatic experiment proved to be a turning point in my thinking. The visions of the many problems on the liver that might now be investigated with reasonable prospect for success made me realize that their pursuit would take so much time I would be too old to become a surgeon. So my dream of becoming a clinical surgeon faded forever, and I admitted to myself for the first time that I was committed to research, to attempt to enhance physiologic knowledge by means of experimental surgery.

After viewing at first hand the efficient and smooth-functioning method of the group practice of medicine, in which physicians with diverse trainings and abilities worked together for the ultimate benefit of the patient, I con-

ceived the idea, which of course was not new, except to me, that the same method should be used in research. I envisaged a group of scientists, trained in research in different fields, working together on problems which required more specialized training than can usually be acquired by one individual. It would thus be feasible to undertake investigations which otherwise would be difficult or impossible. The obtained data and resulting publications would be more valuable because they would have been subjected to expert analysis and criticisms by several individuals. The researches on the dehepatized animal, which required technic and knowledge in which I had great deficiencies, increased the desire to make the vision real.

The completion of a new experimental laboratory (The Institute of Experimental Medicine of the Mayo Foundation) located in the country in order to eliminate some of the problems relating to the laboratory animals, afforded the opportunity to try the experiment of group research. The first requisite was the selection of the trained scientists. Each individual not only must have had specialized training in the science he represented, but also be capable of co-operation.

It will not be possible to record here the achievements of the little groups of scientists who were persuaded to work together in our experimental laboratory or the great unpayable personal debt owed to them. I hope to report this in another manuscript at a later date. Suffice it to state that each became outstanding in his own field, and the combined efforts of all assured the success of the experiments in group research. In retrospection, it would appear improbable that a finer, more co-operative group of colleagues could be found. Fortune indeed is sometimes favorable beyond dreams.

The plan executed for group research was as follows: all participants in each group would be equal and function on a voluntary basis; the time required for the group research was limited in order to permit each participant to carry on investigations in his own field and of his own personal interest. The nebulous honor of having his name first on the published paper was granted as an inducement for the member of the team who would do the greatly-disliked task of preparing the manuscript. Of course, each scientist gave his approval of his own contribution and the completed manuscript before publication.

It was found that an investigation to be made by a group required a very carefully prepared design if it was to be successful. The individual experiments had to be scheduled with great exactness. A discovery beyond the preconceived goal, the unexpected discovery, was not so likely to occur as in researches made by the individual. In our work it was not efficient for a group to search for a goal that existed only in the imagination; the direction of the research required a previously discovered guide. The participant in group research has difficulty in living in the classical ivory tower of the scientist. He must have more than one research interest if his time is to be used most efficiently. This latter was surprisingly found to be advantageous in the type of research the laboratory was making. This result appeared to indicate that

the often-cited fact that a man lost in the wilderness always walks in a circle might apply to mental activity as well as physical. The researcher, if he is actually looking for the unknown, must usually be in a wilderness of imaginations and theories, and he may frequently travel mentally in a circle. Two or more interests might serve effectively in breaking this mental circle.

One of the most vexing problems, a common one for experimental research laboratories, related to the procurement, housing, and care of laboratory animals. From the very first my position included the responsibility for all the laboratory animals of the institution, a goodly number. When the fulfillment of this responsibility began to take its toll of my coveted time for research, I was forced to try to find a solution to all our animal problems. The idea occurred that since one of the main difficulties was the prevalence of disease in the animals, the appointment of a veterinarian to the laboratory staff might prove a solution to our animal problems. I made this suggestion to Dr. Wilson, who not only approved it, but suggested in turn that I invite Dr. S. D. Brimhall, who had assisted him in bacteriologic field surveys, to join our laboratory staff. Dr. Brimhall readily accepted the appointment. This was the first time, so far as I am aware, that a veterinarian in his professional capacity had become a member of a research laboratory. This event proved to be a happy solution to our animal problems, and ever since there has been one veterinarian or more on the staff.

It soon became evident that our veterinarian colleagues had much more to give us than just their knowledge and skill in the care of animals. They possessed a type of training which included knowledge of special differences in both function and disease, and the all-important necessity for observation which was of special value. It may not be generally realized that veterinary practice has in some respects made as rapid progress as the practice of medicine among human beings; that many hospitals for pets and domestic animals as well as animal clinics have been developed which are just as functionally satisfactory as the best hospitals for the human being; that such advances in veterinary medicine have had considerable influence in improving the housing and care of laboratory animals, that the faculties of veterinary schools include many worthy scientists and the physiology departments of such schools are potentially important for researches in comparative physiology, a field which once flourished but has suffered from neglect.

Dr. Wilson assigned a fellow of the Mayo Foundation to work in the laboratory a few weeks after my arrival, and from then on there were always several graduate students in the experimental laboratory. Altogether, there have been in our laboratory, working under the direction of my colleagues and myself, several hundred graduate students, mainly composed of fellows of the Mayo Foundation. Although the investigative work was classified in the various basic sciences upon which the practice of scientific medicine depends, most of the investigations could rightly be considered researches in physiology. In a majority of the instances, the research was but a part of the fellow's graduate training in preparation for the practice of medicine, sur-

gery, or one of the clinical specialties. For a small percentage of students, the training was preparatory to a career in research or teaching. With few exceptions, the students had received the degree of doctor of medicine and subsequently had spent one or more years working in the hospitals. Most of the medical schools of the United States and Canada, as well as many schools of other countries were represented by one or more students. Approximately half of the group completed the thesis requirement for the degree of either master of science or doctor of philosophy.

At first I personally resented the intrusion of the fellows in the laboratory because I felt they were taking time which could more profitably be spent in my own researches. However, the experiences with a few of the fellows, who had keener minds and better training in many respects than myself, made me realize that I had readily at hand a continuous flow of untapped imagination and willing hands that could be readily trained. I found that the graduate sudent can bring a season of spring to the laboratory, a stimulus to budding, growth, bloom, and fruition. In the end, the educational phase of my work became more interesting and appeared to be more important than the researches; the appreciation of a student associate in the research more valuable than a discovery.

At the first interview with a fellow assigned to the experimental laboratory, his future plans, previous training, and special interests were discussed. Very few of the fellows had had previous experience in research and rarely did they suggest a problem. Then different problems in the field in which a preference had been indicated, problems which appeared to be worth while and which could be completed within the time the fellow could spend in research, six months to a year, were presented. Fellows majoring in surgery desired problems requiring a maximum of surgical technic and a minimum of anything else, while the fellows majoring in medicine preferred problems in physiology with a medical objective which required little work in other sciences, such as chemistry.

It was occasionally difficult to initiate some individuals in research because of their belief that problems no longer existed. A discussion of any specific problem was frequently quickly followed by another visit of the student, bringing his textbook, for the purpose of proving that the problem discussed had been solved. This condition appeared to be the result of such thorough previous instruction that he had acquired the view that all the facts were known. He had failed to learn that much that is considered true is relative with time; that science is dynamic and constantly changing as the result of observation and experimentation; that a discovery, a change in technic in quantitation or detection in any of the physical or biologic sciences might quickly relegate to history a paragraph or page from his cherished textbook.

One of the first questions that a student, embarking upon his initial research, frequently asks has to do with the probable number of experiments he should perform in order to finish the investigation. This is also a problem to

all investigators. It was in connection with such a question that the policy previously mentioned in regard to the design of an investigation proved valuable. In case of doubt, the data were submitted for review by the colleague, who probably would be best advised and who would be the most critical of the result dealing with the specific research.

The fellows assigned to work with us usually proved to be very keen students. They would ask many questions, some of which I could not answer. This was very humiliating, and various expediencies were tried to hide my ignorance. This only served to make more confusion. An observation of the working methods of my clinical colleagues supplied a very successful answer to this irritating problem. It was evident that the clinician does not decrease in his professional stature or dignity when he refers a patient to another physician, although such an act is a tacit admission that he does not know everything about the practice of medicine. It was equally evident that a researcher should not be expected to know everything that an inquiring, imaginative student might ask. I soon found it easy to say, without loss of dignity, that I did not know the answer to such questions, but that we should find out. If a review of the literature did not give the answer, the problem was placed on the agenda for experimentation. Estimation of the value to a fellow of carrying out experimental research was a recurring problem; a question of whether or not the research time could not with more profit be spent in clinical apprenticeship. The objectives of the fellow were definite: to secure the necessary material to fulfill the requirement for an advanced degree; to make a valuable discovery; and to obtain training in research. However, laudable as the objectives might be, it was recognized that the thesis requirement was designed originally for the training of the specialist in the field limited by the boundaries of the problem. Such restriction appeared rather antiquated judged by current trends in graduate education, especially as related to medicine. It was perceived, too, that the little discoveries made by the fellow usually would fall far short of ever reaching the clinic or the bedside of the patient. It was not hard to see that the plans of the fellow had to do with the stethoscope and the scalpel, and not with the accoutrements of the research laboratory. It finally became clear that the researcher was ignoring the educator; that so far as the graduate student was concerned, the more important value of research related to education and not discovery.

Hence, I have come to consider research, using the term in a broad sense, as an inseparable part of the process of higher education. Instruction develops the body of a subject, but it requires research to give it life. This view is particularly pertinent to the physician. The practice of scientific medicine, because of the results of research, is dynamic, not static. It is never quite the same today as it was yesterday or will be tomorrow. The medical graduate must go forward or backward; he cannot stand still, much as he may desire to do so. I am of the opinion that the pursuit and completion of a problem in research constitutes the most important single phase of his education, conducive to stimulating him to keep up with his profession.

In a growing and progressive developing science or profession, many of the supposed advances are false. This situation is inevitable if progress is to be achieved. Only the dead commit no errors. However, if the medical practitioner is to give his patient the benefit of the advances in his profession and at the same time protect the patient from unwarranted experimentation, he must be able to judge between the true and the false in the mass of reports of new discoveries and so forth that reach his desk in his journals and are presented at the meetings of his professionai societies. From my observation of the young men who have worked with me in research, I am of the opinion that spending a period of time in a research laboratory affords the young physician the best training for correct evaluation of the new things presented for use in the practice of his profession.

An often-made query relates to the value of an experimental research laboratory as an integral part of a clinic. This question is of more significance now than at any time of the past, because of the ever-increasing number of experimental laboratories being established at clinics or in hospitals. The obvious function of the experimental laboratory is to make a discovery which will be of benefit to the patient, but calculation reveals that the number of investigations which reach this goal are disappointingly small. I believe that the experimental laboratory has possibly a greater worth than the total of discoveries made in it. If the patient of tomorrow is to receive better treatment than the patient of today, the spirit of medical progress must be maintained. The experimental research laboratory is among the first, if not the most important, factor in sustaining that spirit of progress.

The current period arrives, a period in which the fame of research and experimentation is universal; a period characterized by many changes, such as the rapid development of intricate and amazingly successful apparatus and technics for research and teaching in physiology; a plethora of monies; a great increase in well-equipped laboratories for research; the institution of the project type of research which has been responsible for many valuable additions to the temple of physiologic knowledge, but too often has contributed only gingerbread; the increasing employment of the methods of statistics, that happy marriage of biology and mathematics which has been so productive of valuable physiologic progeny but still gives birth to many offspring which are significantly lacking in evidence of a biologic heritage; the entrance of physiologists, growth of physiologic research, and application in clinical medicine and medical specialties beyond the dreams of Meltzer, but not beyond his censoring when the clinical investigator becomes more researcher than physician; the recordings of much physiologic data and conclusions in diverse publications which excite the admiration and wonder at the rapid progress of the science of physiology but on rare occasions leave a feeling of incredulity, that as physiologist I am reviewing the remains of scientific debris much as the merchant must have viewed the results of the classical bovine in his china shop.

Thus the story is ended, and in retrospection raises a serious doubt that

it is worth while or has achieved the stated objective because the greatly changing times have made futile attempts to charter the future by the past. It is admitted that nothing really new has been presented, as any physiologist with experience in research and teaching will recognize; that the ideas expressed are based upon experience and general impressions, the most ignoble pitfalls of a scientist because experience may be nothing more than the result of making the same error repeatedly and general impressions are often mental artifacts created by wishful thinking.

An investigator in our present world, in spite of the widespread favor of research, has a part which is all but insignificant in a vast and rapidly progressing movement. The outlook for the research-minded is portrayed vividly but probably truly by Kubie (9), down to the most pessimistic detail. The impact of current conditions upon human affairs has been disrupting, but it is questionable whether the scientist has been affected any more than many others. It is possible that security is not the most desirable objective in life, that chance favors the scientist as often as individuals in other professions and occupations, and that the nurturing of frustration (which is probably the greatest cause of unhappiness of the scientist and teacher), the fear of failure, and the lack of self-esteemed rewards can be quelled by the recognition that doing what one desires most to do is probably the most important single factor to consider in the selection of a career.

It is certain that physiology can be a living subject for the true teacher, the one who lives in the memory of his students long after most of the specific things he taught are forgotten or made historic by research. Physiology also has a research goal probably impossible of achievement: to discover life and whether it is more than a happenstance of physical factors with the dance of intracellular enzymes.

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TRANSPORT THROUGH BIOLOGICAL MEMBRANES[1,2,3]

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Highlights of the Biennium

Tissue osmotic pressure *in vivo* equals that of the blood plasma (123, 124, 125). The voltage-controlled frog skin sets a research pattern (113, 117). The energy requirement of ion "pumps" is lowered (39, 81). The kinetics of erythrocyte ion carrier mechanisms is defined (81); K and Rb, Na and Li compete for common carrier systems (81, 88). The Na-rich cell is a model test object (37). The cardiac glycosides retard Na extrusion from Na-rich erythrocytes (87) and frog sartorius muscle (38). Increased Na in sartorius fibers lessens the "overshoot" of the reversed polarity action potential (43). The "staircase" of muscle results from lowered fiber K (47, 48, 49). The K release of muscle contraction is a true pulse (44). Plasma alkalosis may result from a shift of H into K-poor muscle (40). Lowered Cl in the medium reduces fiber K (34). New equations describe transcapillary (136) and transglomerular kinetics (141). An "indicator dilution curve" is used as a test for capillary permeability (148).

Reviews.—Membrane transport by Ussing (1); electrolytes in fluids and tissues, very exhaustive, by Manery (2); capillaries by Pappenheimer (3); water by Pinson (4) and by Robinson (5); renal sodium by Selkurt (6); K-deficiency by Nadler (7). *Symposia*: Potassium (8); ionic transfers basic to kidney (9); enzymes in membrane transport (10). *Monographs*: Exchange rate by Ussing (11); tissue buffering by Pitts (12); potassium accumulation by Ling (13); isolated frog skin by Linderholm (113).

In memoriam. Rudolph Höber, 1873–1953 [Amberson (152)].

The Pitfalls of Exchange Studies

Each new monograph on the calculation of isotopic exchange rates hints that the author has joined the age of disillusion, has awakened to the fact

[1] This review includes literature over the period May, 1952 through June, 1954' for the topics listed. Other topics will be found in other chapters for 1954 and 1955'

[2] The following abbreviations have been used in this chapter: ATP (adenosinetriphosphate); DCA (desoxycorticosterone acetate); ACTH (adrenocorticotrophic hormone); DNA (desoxyribonucleic acid); DNP (dinitrophenol); TEPP (tetraethylpyrophosphate); DFP (di-isopropylfluorophosphate); P. D. (Potential difference); S.E. (Standard error).

[3] This was prepared during the tenure of a research contract (AT-40-1-1301) between Tulane University and the United States Atomic Energy Commission.

[4] I am indebted to Dr. Irene Bay for expert aid in the search for titles.

that the estimation of exchange rate in tissues by isotopes does not yield the lush harvest he had envisioned. A prime requirement is the quick presentation to the cell surface of a known steady isotope ratio (specific activity) which is to travel into the cells. A second question is that of the assumed instant and homogeneous mixing of the isotope within the cell compartment (protoplasm). All mathematical analyses to date, such as that of Sheppard & Householder (14), assume this. Let us hope that more realistic, though involved, mathematical approaches can be invoked which describe diffusion of the isotope through successive fringes of protoplasm from exterior to interior. If multiple exchange compartments exist within a cell or tissue, with the sequence of exchange from one to another unknown, mathematical analysis is difficult or impossible.

Both of these difficulties disappear with use of certain multicellular membranes. Homogeneous samples can be collected on both sides of the isolated frog skin [Ussing (11)]. With a slowly exchanging system like aqueous humor, Na^{24} transfer can be charted over a long time course after the plasma level becomes steady [Wilde & Scholz (15)]. Use of isolated cells, such as erythrocytes [Sheppard & Martin (16)], allows quick mixing of the isotope into the medium, but cell preparations isolated from tissues such as the liver [Ginsburg (17)] encounter the throes of survival in artificial media.

Work with isolated tissue slices and muscle strips involves a slow diffusion of isotope through extracellular space as considered mathematically by Harris & Burn (18) for the frog sartorius. Keynes (19) introduces a small toe muscle from the frog, a 0.5 mm. cylinder containing 60 fibers. The rate correction factor for the diffusion of isotopes through the extracellular space is only 10 per cent compared to 33 per cent for the sartorius. In the toe muscle (19) K exchange works out nicely. However, the extracellular washout of Na^{24} fuses, when plotted on a log plot, into the slow curve for cellular exchange. The entire time course is curvilinear, and the choice of the slope for cellular exchange is arbitrary. Johnson's use of a simultaneous washout of Na^{24} and radiosulfate seems promising (20). Tissue slices, as from the kidney or liver [Mudge (9)], may not possess homogeneous extracellular phases because of occluded tubular urine or capillary bile. They also face the problem of survival in artificial media.

In the perfused preparation, inflowing specific activities are held steady and extracellular fluid is quickly equilibrated with tag to present a steady specific activity to the cells. Very early the failing circulation may result in areas being shut off from the exchange. In this laboratory we have noticed that the "indicator dilution curve," delineated as an injected slug of radioactivity traverses the heart coronary bed, is a delicate indicator of the state of the vascular bed in perfused organs. The curves deteriorate noticeably during perfusion for an hour. Leong, Holloway & Brauer (21) find that K^{42} behaves as though it equilibrates into only 80 per cent of the perfused liver. Theirs is an unusually viable preparation.

Isolated tissues, immersed as well as perfused, often show nonexchanging

K fractions, whereas the same tissues in intact animals do not (25). Relative exchangeability of K may indicate degree of viability. Harris (22) finds that Creese's bicarbonate medium (23) sustains K in sartorii, but even after 18 hr., apparently exchangeable K, highly variable, is only 62 per cent of the total. This exchangeable fraction enlarges when external K or phosphate is elevated. The frog toe muscle used by Keynes (19) contains 97 per cent exchangeable K. Calkins, Taylor & Hastings (24) report remarkable success in maintaining rat diaphragms. After a rapid loss of K (15 to 30 per cent), which leaks unmistakably from cut fibers, K level remains constant and is 97 per cent exchangeable to K^{42}. Insulin induces deposition of 4.5 μM K with 1 mg. glycogen.

Studies of tissue exchange rates in the intact animal after intravenous or intraperitoneal injection of the tag might seem to obviate some of these difficulties. There is no question of tissue viability, and the irrigation of extracellular space is rapid. Ginsburg & Wilde (25) have charted the scatter of intravenous K^{42} into rat tissues. Declining plasma specific activity is fitted to the mammillary equation of Sheppard & Householder (14). The several exchange masses of body K predicted from the constants of the fitted curve do not correspond to chemically analyzed masses in actual organs. The possibility of more than one exchange mass in any single organ is discussed. Any one of these masses may possess an exchange equal in rate to a mass in other organs. These may summate among the different organs and appear as a common mass expressed in the analysis of the plasma curve. Analysis of exchange rate in any one tissue is complicated by the shuttle of tag to and fro between it and other organs of slower and faster exchange rate. The curve for isotope movement into a given organ contains exponential phases for all other compartments in the animal. It is difficult to estimate which phase or phases is typical for the given organ. All the K in every organ seems completely exchangeable. Love, Romney & Burch (26) present a similar exhaustive mathematical study of rubidium Rb^{86} in the dog. The very slow radioactive decay contrasted with K^{42} allows delineation of the slowest exchange masses and of late excretion rates. Detailed results are strikingly parallel to those for K^{42}.

For very rapidly exchanging isotopes, such as D_2O applied to all tissues [Johnson, Cavert & Lifson (27)] and K^{42} to the kidney [Walker & Wilde (28)], the isotope leaves so completely and early down the course of a capillary that the exchange rate of the tissue is not really tested. Uptake of tag by the organ is limited by the circulatory irrigation. Mathematical considerations are given by Sheppard *et al.* (29) and by Sheppard & Sangren (30).

Electrolytes in Muscle

Working hypothesis for ionic accumulation.—The working hypothesis [Dean (31)] most commonly invoked to explain ionic composition of muscle is an active extrusion of Na combined with passive diffusion inwards of K as KCl [Boyle & Conway (32)]. Enthusiasts who insist upon "pumps" for

all ions should continually check their results against the physical chemical principles described by Boyle & Conway. Much useful physical chemistry is also elaborated by Ling (13) in his "Fixed Charge Hypothesis." Because of its smaller hydrated radius, K is selectively adsorbed over Na upon fixed anions including ester phosphate associated with contractile protein. Energy is used, not to operate ion pumps, but indirectly to maintain ester phosphate as preferential anionic adsorption sites, "energy wells," for K.

Passive KCl.—Conway's evidence for his modified Donnan relation $K_1 \cdot Cl_1 = K \cdot Cl$, is that highly elevated K in the medium (right term) drives Cl into the fiber (left term). Lukowsky & Netter (33) avoid possible membrane damage by selecting that "threshold" external K level, 8.6 mg. per cent, required barely to maintain internal fiber K. Instead of elevating external potassium, Kusel & Netter (34) lower external Cl by substituting sulfate (an impermeant anion?). Potassium leaches out of muscle somewhat in proportion to lowered external Cl. If nitrate, also a permeant anion, is substituted for Cl, K does not leach out. A lowered external Cl will even prevent an elevated external K (40 mg. per cent) from driving potassium into the fiber. Such jockeying, K upward and Cl downward, can be imposed without causing internal K shifts as long as their product $K \cdot Cl$ outside remains constant. Passive penetration of K and Cl as paired counter ions is presumed. External Cl levels alone should not influence possible carrier systems for potassium or sodium. Perfusion enthusiasts will find an interesting computation (34) of extracellular space [Note typographical error: $X = 1 - [(A - C_n)/A]^{\frac{1}{n}}$. Unfortunately instantaneous mixing between blood vessels and interstitial fluid is presumed.

For Ling, as for Conway, K^{42}-labeled KCl may move across the membrane into total muscle water. After brief equilibration of frog sartorii, the $K^{42}Cl$ should then wash out into inactive RbCl with higher K^{42} specific activity at first than later [Ling (35)]. Such behavior may explain an early fast phase of a two-stage K^{42} uptake, particularly when the more quickly exchanging K mass represented is several times larger than that found in the extracellular fluid [Harris (22)]. If such a passive membrane traversal of KCl were a controlling rate for exchange of the entire K, then total influx and outflux of K should be proportional to external K concentration. For Keynes (19) elevation of outside K from 2.5 to 5.0 mM accelerates influx from 4.1 to 7.3 and outflux from 4.9 to 8.6 $\mu\mu M$./sq. cm. of fiber surface/sec.

Na extrusion.—Steinbach finds (36) that isolated frog sartorius, once rendered Na-rich and K-poor through immersion in K-free media, can again extrude Na and accept K on return to normal K Ringer. Wondering whether re-uptake of K is passive, conditioned by prior Na extrusion, he has tried displacing Na and K with choline (9, 37) in a low-K, low-Na medium. The choline displaces Na down to 8 m.eq. per kg. muscle, K down to 33 m.eq. When these muscles are placed in normal Na-K saline, K will not go back in. Any projected K carrier will not carry K back into the fibers. There is no carrier to move choline out, as it might otherwise move Na, and let K come in-

ward passively. The fibers are not dead, since NaCl does not diffuse inward.

Using the Na-rich sartorius for a study of potentials (see below), Desmedt (43) charts the time course of Na extrusion, which follows an exponential. The number of moles of Na travelling outward is related to the inside Na concentration. Does the degree of loading of anionic carrier sites depend upon internal Na concentration? It is less clear whether concomitant K uptake occurs at a constant rate or at a declining exponential rate. Coupling of K and Na movements is not excluded. Further attention to this problem might be fruitful.

This Na-rich, K-poor muscle preparation promises to be useful as a test object for hormones, drugs, etc. Johnson and Matchett (38) note that 1.1×10^{-7} *M* ouabain allows K uptake but no Na extrusion. Stronger doses block K uptake also.

Energetics of the Na extrusion.—Previous thermodynamic calculations have shown the active Na extrusion from muscle fibers to incur an uncomfortably large share of the resting energy outlay. By doing simultaneous oxygen and Na^{24} outfluxes, Keynes & Maisel (39) pare this down to 10 per cent of the resting energy in frog sartorius. Lowered external K heightens the resting membrane potential (positive outside). Na extrusion against this increased electrical gradient is retarded and less oxygen is used. If external K is elevated toward 10 m*M*, the potential falls and Na extrusion is accelerated up to four times. Even with the lowered potential, because of the increased Na outflux, more calculated energy is needed and the increase in O_2 consumption percentage-wise is about the same. No muscle contracture occurs. Potassium elevation also increases K influx and outflux (19). This does not deny direct coupling of Na outflux and K influx on a carrier system. However, Na and K shifts in K-deficient muscle (40) are not unalterably linked; hydrogen substitutes temporarily for K in the exchanges. Harris (41) finds a weak increase in Na outflux when the initial length of the sartorius is stretched so as to increase energy production. This does not affect K fluxes (22) so that mechanical effects upon extracellular irrigation are somewhat excluded. If the phosphate that leaches from resting muscle (1 μM/hr./gm.) arises from ATP^2 the energy yielded is sufficient to extrude but 3 Na atoms out of the 10 actually extruded [Harris (42)].

Ion movements and potentials.—Desmedt (43) confirms Steinbach's (36) observation that sartorius fiber Na is elevated in low-K media and extruded in normal K-media. The Ling-Gerard intrafiber microelectrode records the reversed potential of the action current as positive inside (the "overshoot"). The overshoot shortens as internal Na concentration rises just as it does if external Na is lowered. This follows the Hodgkin & Huxley (45) concept of the role of Na in the genesis of active membrane potential. In the electrocardiogram, such changes induced by K deficiency may explain changes in the T wave and S-T segment.

Tetanic stimulation of muscle over time releases muscle K [Fenn & Cobb (8, p. 163)]. O'Brien & Wilde (44) now show that a single systole of heart

muscle produces a distinct pulse of K release. K^{42} in a highly pre-enriched turtle ventricle is carried by the coronary perfusate onto a traveling filter paper strip, which is cut into timed segments for radioactivity counting. A constant level of a second radioactivity is added to the perfusate to act as an indicator of volume of outflow caught on each sample segment. The plot of K^{42} concentration in the outflow against time is called an effluogram. A distinct K^{42} concentration wave extrapolates backward, because of the coronary travel time, to coincide with the late part of systole and with the repolarization T wave. This follows the prediction of Hodgkin & Huxley (45) based on changes in membrane current as influenced by external K concentrations. The release may likewise be related to the contraction process.

Keynes (19) could attribute only one-sixth of the total conductance across the sartorius membrane, as measured by microelectrode, to the isotopically measured mean flux of K. Harris (46) finds by ionophoresis of K^{42} along a sartorius muscle placed in an electric field that the rate of migration of the K ions is from 80 to 100 per cent of that in water solution.

Potassium and contraction dynamics.—"Staircase" in frog ventricle is a sequence of contractions each of which is stronger than the preceding, mimicking a staircase on the record. Bowditch reasoned that each contraction leaves behind in the fibers a condition more favorable to develop the next stronger contraction. Hajdu (47) by direct analyses finds that this favorable condition is a lowered K or Na content. As averaged from 30 beats of a heart treated with digitoxin to retard the recovery influx of K, the release of K per beat is 127 μM. from each liter of fiber water. The tension developed increases linearly as the K content declines over a range of 3 m.eq. beginning at a base line of 106.8 m.eq. Na+K per liter fiber water. Na losses over this small range also strengthen the beat. It is the amount of Na+K per fiber, not the concentration, that is effective. Each unit of contractile actomyosin acts with relation to an optimum amount of cell base. When an isolated heart is quiet, it accumulates K so as to exceed the optimum. Then as it is set into a sequence of beats, each beat releases K and renders the K content more nearly optimum for the next beat. Digitalis may retard K re-entry and thus favor stronger beats.

Horvath (48) relates K and Na contents of rabbit uterine muscle to vigor of contraction (staircase). Csapo & Corner (49) and Csapo (50) suggest for rabbit myometrium a relation between K and staircase similar to that described in frog heart by Hajdu. Estrogen-treated myometrium (48), having a high K (158 mM in cell water) and low Na (30 mM), yields positive staircase or increasing vigor during rapid serial stimulation. Possibly the high K is above the optimum and then leaches out toward optimum during each successive contraction giving the rising staircase. Progesterone-treated muscle, having lower K (132 mM) and higher Na (45 mM), develops negative staircase or decreasing vigor with successive rapid stimuli. Csapo would interpret these muscles to possess sub-optimum K which leaks out further during the contraction sequence thus weakening the contractions.

The exchange of H, K, and Na.—An enigma of recent years turns on the question how much of the alkalosis of K depleted animals is to be assigned to tissue as against renal events. Cooke *et al.* (40) assign the initial event to tissue (muscle) cells. Approximately two Na and one H ion exchange into muscle fibers as three K ions are drained away during K deficiency. The departing H ions leave hydroxyl (bicarbonate) behind in the extracellular fluid. Proof lies in urinary balance studies done while the deficiency is repaired by administering known KCl. As the added K exchanges into muscle, H moves out to join the chloride. Enough HCl appears not only to neutralize the alkaline extracellular fluid but to acidify the urine and incite ammonia formation. Orloff, Kennedy & Berliner (51) provide direct evidence by giving KCl to K-deficient rats after nephrectomy. Plasma bicarbonate and pH fall as K shifts into muscle. Muscle of K-deficient rats has slightly diminished CO_2 content, yet total base, because of Mg and Ca increase, is unchanged over controls [Gardner & MacLachlan (52)] in blood- and fat-free, dry muscle. Wallace in an oral report says total base is lessened from 204 to 188 m.eq. per liter of cell water (9, p. 49). Once a plasma alkalosis of tissue origin has developed the kidney cannot repair it. Wilde (53) reviews Berliner's explanation (54), that with deficiency of K in the plasma, K competes unfavorably with H for renal secretion so that the kidney cannot place plasma alkalinity, as $KHCO_3$, into the urine. Roberts, Magida & Pitts (55) wonder if reabsorption of bicarbonate as such is not directly influenced.

When a low protein diet is combined with a low K diet [Muntwyler, Griffin & Arends (56)] rats grow slowly, but they do not go into K deficiency in any of its aspects, plasma or muscle electrolytes. K coming from metabolized tissue protein replaces K absent in the diet or lost to the urine. With less protein being deposited, the call for tissue cation is less. If now protein is given suddenly to these animals, muscle grows suddenly and develops a rapid K deficit, but muscle Na does not elevate and the plasma hypochloremic alkalosis does not appear. The authors argue that H ion should shift into the muscle [Cooke, *et al.* (40)] and that the kidney should be unable to cope with the resulting plasma alkalosis because of plasma K deficit [Berliner (54)]. However, this muscle picture develops quickly and the plasma K is not really low. Plasma K may still be abundant enough to secrete $KHCO_3$ into the urine.

In a significant effort, so far reported only in symposia (9, 12), Swann and Pitts estimate the buffer activity of tissue cells by following the ion shifts in the inulin space of nephrectomized dogs after HCl injections. Of 206 m.eq. HCl given intravenously (12) to dog No. 2, 139 m.eq. Cl remains in the inulin space, which also gains 18 m.eq. K and 70 m.eq. Na or 88 m.eq. of these combined bases, as pH falls from 7.4 to 7.0. This leaves 51 m.eq. HCl to be neutralized by $NaHCO_3$ initially present in the inulin space. Actually 61 m.eq. bicarbonate disappear. Of the 67 m.eq. Cl that leaves the inulin space, 7 m. eq. enters erythrocytes and 60 m.eq. enters other noninulin space. Using Conway's equation $Cl_1 = (Cl/d)K$ (in which d equals total dif-

fusible anion concentration), I estimate that the elevated plasma K could carry 37.5 m.eq. Cl into cell (noninulin) space (57). In dogs 5 and 6 no Cl left (9), but nearly twice as much K and Na entered the inulin space. This could come from muscle or bone [Bergstrom & Wallace (58)].

Axlerod, Seip & Pitts (9, 12) inject variable amounts of $NaHCO_3$ into this same dog preparation. About a third of the bicarbonate anion leaves the inulin space and is replaced by equivalent chloride coming presumably from tissue cells. This mimics Conway's anion distribution in muscle and the chloride shift in corpuscles, or in whatever other tissues it applies. By direct measurement, the erythrocytes themselves account for only about a tenth of the entire exchange. Does this explain the hypochloremia of alkalosis in K deficiency? Schwarz, Cohen & Wallace (59) find that total chloride in entire K-deficient rats does not change but the chloride space increases. Since acid leaches K and Na out of tissues, alkali should do the reverse. Actually no significant shift occurs. Possibly this relates to the marked reduction in plasma K, from 4.45 to 2.67 m.eq. per liter in dog 3, caused by expansion of extracellular fluid. Knowledge of whether the latter occurs in other individual animals must await formal publication of the results.

Cooke & Segar (60) propose a mechanism by which H ion concentration in the medium regulates cell K content irrespective of renal action. Alkalinity drives K into the plasma, from which the kidney removes it causing depletion. As already seen, this is opposite to the results of Pitts *et al.* just cited. Moreover, the muscle of alkalotic, K-depleted but nephrectomized rats takes up injected K avidly (51). Even when $NaHCO_3$ is injected into normal nephrectomized rats [Eckel & Smith (61)], plasma K falls slightly. Predictions from the theory are opposite to Fenn's results *in vitro* (in 8, p. 159). It is not clear whether the authors argue for a carrier system or a passive ionic exchange. Antagonistic trends in exchange are proposed which render prediction uncertain.

Effect of hormones, drugs, vitamins.—Since the response of muscle and tissue electrolytes to adrenocortical hormones is confused by renal events, Woodbury (62) has administered the hormones to nephrectomized rats. The nephrectomized control rat loses muscle Na but gains this back to normal under DCA[2]. Neither state induces K changes. ACTH[2] combined with DCA lowers Na so far that the Cl space exceeds the Na space. K also falls. Does the hormone extrude connective tissue Na such as might associate with hyaluronate in excess of Cl [Mathews (63)], or does it extrude a supposed muscle fiber Na and reveal that Cl resides inside the muscle fibers? Robertson & Dunihue (64) have studied the effects of steroid hormones on cat heart muscle. Dury (65) discusses the very complicated relation between plasma, liver and muscle K and plasma glucose as influenced by insulin and epinephrine.

Holland, Dunn & Greig (66, 67) have tested the acetylcholine mechanism in isolated guinea-pig auricles. K leaks from the control auricle. This leads to the use of a ratio of leakage rates, experimental/control, that is

ambiguous. Acetylcholine seems to increase the leakage; certain anesthetics, to reduce it.

Thiamine deficiency does not mimic DCA completely [Pecora (68)]. Muscle and heart Na elevate, and K declines, but plasma K does not fall.

Technic.—Ray, Threefoot & Burch treat exhaustively the problem of calculating exchangeable "mass" and "space" with isotopes [(69, 70); for Cl^{36} (71, 72)].

An ideal in muscle tissue analysis is to associate measured ionic changes with a fixed number of fibers. Reference of concentrations to wet weight is influenced by the extent of fat, blood, edema fluid, cellular hypertrophy and hyperplasia, etc. DNA^2 content, as representing a given number of nuclei [Micklewright, Kurnick & Hodes (73); Harrison (74)], is a recent innovation over blood-free, fat-free dry weight. Baldwin and co-workers (75) present again their noncollagenous nitrogen (NCN). It presents nitrogen other than that in connective tissue collagen, which latter may increase in disease. Their unit mirrors protoplasm, whereas DNA represents a given number of nuclei or of cells. Biopsied human muscle, referred to 1 gm. NCN, presents marked uniformity in amounts and proportions of K, Mg and PO_4, whether normal, atrophied, or from patients with widespread electrolyte distortion of the serum.

The estimation of extracellular space in tissues and for the entire body is still unsolved [Manery (2); see Cotlove (76) for a thorough critique of inulin and sucrose space]. Barlow & Manery (77) find equality between histological and Cl space in 3-day chick muscle. A chromogen in liver [Williams, Seibert & Huggins (78)] masks the Volhard titration end point for Cl which yields 25 per cent less Cl than a gravimetric method. Muscle Cl space exceeds inulin and at times sodium space (62). Nerve axoplasm contains Cl as do isolated muscle fibers [For discussion see Steinbach (9, p. 28)].

Walser, Seldin & Grollman (79) seem more enthusiastic for a radio-sulfate space in dogs than are Sheatz & Wilde (80) for the same in rats. A species difference could be attributed to many factors: utilization of sulfate by intestinal microorganisms and incorporation as etherial sulfate into connective tissue chondroitin sulfuric acid. A higher level of intrinsic plasma sulfate in one species, by diluting out the tag, could mask these effects. Injection of carrier sulfate may be helpful except for the faster excretion rate.

Erythrocytes

Exchange studies.—Erythrocytes, unlike muscle, may possess a K as well as a Na carriage, only anions including sulfate being passive. Solomon (81) submits a significant isotope study using human erythrocytes. As noted earlier [Sheppard, Martin & Beyl (82)], a K carrier shuttles inward about 1.67 m.eq. K/l. of cells per hr., no matter what the external K level between 4 and 16 m.eq./l. of serum. The carrier seats must be nearly filled normally. Rubidium competes 1.19 times more effectively than K. Cesium, with even smaller hydrated radius, competes very little. Possibly a carrier molecule

complexes more easily with Rb and K than with Cs whose naked radius is larger. The Na influx, computed with some technical difficulties, is 3.08 m.eq. Na/l. of cells per hr. The Na carrier is 60 per cent loaded at 143.5 m.eq./l. external Na concentration. Below this, the carrier loads as a hyperbolic function of external Na remindful of a Langmuir adsorption. Lithium competes only slightly less favorably than Na. Possibly 2.37 m.eq. Na of 7.55 m.eq. total in a liter of washed cells is slowly exchangeable in a different pool. Potassium too (83) may have a fast and a slow pool. The computed energy per hr. for transport of the ions into a liter of cells is 2.8 cal. for K and 6.0 cal. for Na. Since the simultaneous anaerobic glucose metabolism yields 55 cal., the work incurred for transport is not too onerous.

The computation of the K exchange used above, like most others, assumes during the time course of the experiments a steady state whereas in fact a small net gain in erythrocyte K content occurred. Streeten & Solomon (84) recast their figures with this in mind. Their influx values, plotted as ordinates against plasma K level on the abscissa, now lie on the flat horizontal wing of a hyperbola. The K carrier, like that for Na, shows a weak tendency to saturate at higher plasma K levels. At the average normal plasma K level, 4.65 m.eq./l., the influx is 2.09 m.eq./l. of cells/hr. Frazier, Sicular & Solomon also have data for dog erythrocytes (85).

Love & Burch (86) have done similar studies with long-lived Na^{22} to evaluate the human erythrocyte as a model of Na metabolism in the tissue cells of patients. Though their data show an average of 1.5 m.eq. Na/l. of cells to be nonexchangeable, they consider this within the error of measurement. Only one patient with high cell Na showed definitely nonexchangeable Na, 7.9 out of 13.8 m.eq./l. of cells. Any Na complexed with a carrier system would be mixed with Na^{22} during the transfer. Very high external K lessens Na exchange as it does the cell Na content. Contrasted with the result of Schatzmann [See below (87)] on Na-rich cells, the flux in normal cells is unchanged by lanatoside C, and by epinephrine, neostigmine, pitressin, cortisone, and DCA^2.

Love & Burch (88) test whether Rb^{86} and Cs^{134} mimic K^{42} in exchange into human erythrocytes. Rb exchange rate equals K which is five times the rate of Cs. Each ion competes with the other for transfer in a carrier system that has a limited capacity. The Q_{10} of each is about 2.27. The equilibrium distributions between plasma and cells are equal for Rb^{86} and K^{42}. The cells deteriorate *in vitro* before Cs^{134} is well mixed; but if its early exponential decline in plasma is extrapolated, a distribution similar to K is predicted.

Effect of pH.—Parpart & Green (89) warn that the dependence of K retention in erythrocytes upon glucose utilization may relate to the influence of concomitant pH changes, because of lactate production, upon the cell surface rather than upon energy considerations. The usual weakly buffered medium turns acid just as the glucose effect begins. Buffering the medium at pH 6.5 undoes glucose protection without retarding glucose utilization. Iodoacetate and Na fluoride [Green & Parpart (90)] accelerate K loss equally with or without added glucose. Thus the effect is independent of the level of

glucose energy supply and the latency of its action is of constant duration regardless of the degree of glucose depletion at the time of application. They emphasize the possible role of pH in regulating molecular orientation within the membrane rather than its influence upon a carrier system (91).

Drugs and hormones.—A recent effective experimental design places the Na-K carriage under stress. Erythrocytes, incubated in the cold, lose K and gain Na. On return to glucose media at 37° C., sodium is extruded and potassium re-enters the cells. Agents which influence this reversal may be applied and quantitated. Cardiac glycosides [Schatzmann (87)] block Na extrusion and K re-entry. Energy production as mirrored in oxygen utilization is increased slightly at first and glycolysis, as evinced by CO_2 production, is unchanged over the control level. Obviously the over-all energy source is not attenuated as it is with iodoacetate or NaF and the cells remain viable. Moreover, the energy requirement now allotted to cation transport is small enough that it might not be even noticed as missing from the total energy ledger. Schatzmann dismisses the possibility that passive back diffusion of cations increases in the face of successful carriage up the gradient. Treating cold-stored cells with glycoside does not accelerate down-gradient migration of the cations. Since over-all energy production is not affected, the block must be close to or within the carrier system itself.

Streeten & Solomon (84) find a mild gain, not a loss, of erythrocyte K after slow (8 hr.) infusion of ACTH, cortisone or hydrocortisone. If these cells are removed from the subject and the flux determined *in vitro*, both influx and outflux are diminished slightly. If hormone is added to erythrocytes *in vitro*, both fluxes are reduced slightly; but no change in K content occurs.

Acetylcholine mechanism.—Greig, Faulkner & Mayberry (92) continue studies relating acetylcholine to K retention in red cells. Human cells suspended in 0.1 *M* $NaHCO_3$ partially hemolyze. The remaining cells, calculated as not having lost Hb, gain Na and lose K. Added acetylcholine (0.01 *M*) retards and in part reverses the ion exchanges. Physostigmine inhibits this protection. Replacement of K into cells during glucose metabolism is likewise blocked by physostigmine. According to Taylor, Weller & Hastings (93), cholinesterase inhibitors, physostigmine and DFP^2, induce loss of K by retarding influx; while choline acetylase inhibitors, methylene blue, and 2-methyl-1,4-naphthoquinone, cause K loss related to accelerated outflux. Thompson & Whittaker (94) begin with Na rich erythrocytes stressed by cold and study Na extrusion in warm glucose media. Na entry in the cold is retarded to half its normal rate by *p*-nitrophenyl diethyl phosphate (E 600) but there is no effect on Na extrusion. DFP remains actionless. Mathias & Sheppard (95) together with Cohn (96) question the import of acetylcholine metabolism in K transport. They find only 0.08 γ acetylcholine per ml. of cells and no increased synthesis in the presence of cholinesterase inhibitors. *In vivo* hydrolysis of acetylcholine, considering its maximum rate of synthesis, could provide only one-fiftieth of the energy required for K carriage as estimated by Solomon (81).

Physical chemistry.—Harris & Maizels (97) elucidate the passive physical

chemistry of Cl and H ions that overlays the active transfer of Na and K. Since, unlike (?) in muscle, K moves actively, it cannot experience an inverse Donnan ratio; $K_i/K_0 = 35/1.0$ is much larger than $Cl_0/Cl_i = H_i/H_0 = 1.4/1.0$. Inside the cell Na and K are equally effective counter ions to associate with Cl and bicarbonate. Metabolic changes influence the ion carriages for Na and K in such a way that the changes of K and Na tend to be equal and opposite, their sums thus constant, and the anion sum associated with them constant. A slight discrepancy comes from dephosphorylation which actually leads to a gain of anion in the cell. Cell base cannot leave with the phosphate freed, which actually exchanges outward for chloride or bicarbonate coming inward. Increased H ion releases base from cell buffer such as Hb, and chloride and bicarbonate move inward. The base released from cell buffer may reach 54 m.eq./l. of cells for a pH change of 1.0.

I have shown by appropriate algebra that the concentration ratio, HCO_3^-/Cl, equal in erythrocytes, extracellular fluid, and tissue cells (?), is equal to the ratio of the sum total of moles of each anion in all three compartments. Since total body Cl is a constant within one breath cycle, only change in total body bicarbonate changes the ratio. The amount of each anion inside an erythrocyte depends both upon this ratio and upon the amount of base, Na plus K, present inside the erythrocyte as counter ions and susceptible to release from Hb by H ion.

Love & Burch (98) again find entrance of Cl^{36} into red cells too fast to measure (99). Low temperature and metabolic poisons seem without effect so that a passive Donnan relation remains applicable. Giacomello (100) confirms earlier work (80) that radiosulfate penetrates the red cells. Contrary to earlier reports, added chemical sulfate also distributes itself about as Cl.

Phosphate.—Gourley (101) continues to find evidence that inorganic phosphate enters eyrthrocytes by way of the labile P of ATP[2]. With human cells in P^{32}-labeled plasma phosphate, the labile P of ATP is enriched faster inside the cell than are other acid soluble phosphates. Cellular inorganic phosphate is next to ATP and the other esters are slower. Cellular inorganic phosphate is the first to reach equal enrichment with ATP. This does not exclude direct diffusion of phosphate into the cell, but ordinarily plasma and cellular inorganic P do not show equal concentrations such as diffusion would imply. The same concentration (102) of iodoacetic acid (IAA) or of sodium fluoride that reduces phosphate uptake to one-fifth of its normal rate reduces ATP to 10 per cent of its normal content and also reduces its turnover rate inside the cell. The plasma gains inorganic P from the erythrocytes, probably from ATP breakdown. After 3 hr. exposure to IAA, cell inorganic P is three times as radioactive as ATP. Does tagged inorganic P diffuse into the cells? This should be tried over a time course. Other work has been done with rabbit and chicken cells (103). Ermans (104) tags rat red cells with $P^{32}O_4$ *in vitro* and then injects them into donor rats pretreated with thyroid-active chemicals. Propylthiouracil depresses and thyroxine accelerates PO_4 outflux over normal.

Miscellaneous.—Tagged alcohols and H_2O^{18} seem to mix into all the water

of erythrocytes [Hutchison (105)]. Several articles have appeared on membrane structure (106, 107, 108), on the effect of abnormal solutions (109, 110) and on the behavior of erythrocyte ghosts (111, 112).

Frog Skin

Surviving frog skin, in the hands of Ussing (1, 9, 11), Linderholm (113), and Huf & Wills (114), becomes a living model of all that is new in membranes. A carrier shuttles chiefly Na from outer epithelial to inner chorion side which becomes positive, attracting chloride inward (115). The charge drags chloride through the skin passively. Usually the passive skin resistance is low enough so that Cl follows quickly, reducing the membrane charge. Skin potential falls when Cl influx quickens (114, 116) even if Na also is moving inward more rapidly. With higher skin resistance, Cl lags behind Na and higher P. D. develops[3]. These views derive from the earlier results obtained with the classic "short-circuited" frog skin [Ussing & Zerahn (117)]. When the overall potential across the skin is "clamped" at zero by an externally applied voltage, only Na can set up a net flux, influx being greater than outflux. Other ions, K and Cl, move passively with equal fluxes in each direction. With no potential to influence them, they now move by diffusion. The measured current that flows across the clamped skin is equal to the net Na flux (influx minus outflux). Ussing thinks of the Na transfer as constituting a "sodium battery" that has its own electromotive force (E_{Na}) and internal resistance (R_{Na}). It is useful to consider how metabolic inhibitors affect these computed values [Ussing, see (9), p. 98]. Inhibitors mostly lower E_{Na} and increase R_{Na}. These views predict a large back leakage of the transported ion against the carrier system. In the bull frog kidney, Na^{22} moves backward from peritubular capillary blood across the tubule epithelium into the lumen [Visscher, see (9)] opposite to the direction of net movement surmised from clearance methods.

The Na carrier is retarded by the uncoupling of oxidation and phosphorylation with DNP[2] [Fuhrman (118); Levinsky & Sawyer (119)], by some cholinesterase inhibitors such as TEPP[2] [Kirschner (120)], by cyanide and caffeine (119). The latter workers find that caffeine lessens Na transport 50 per cent before affecting Q_{O_2} at all. The energy requirement of the Na pump is much less a part of total available energy than was first thought.

Beginning at from 30 to 40 mv. positive charge inside, K is repelled passively to the outside [Huf & Wills (114)] in proportion to further rise in potential. Below 30 mv., the net flux is inward. Is there a weak K carriage inward that is ordinarily overcome by the Na potential? Contrary to this conclusion is the equal influx and outflux observed when the potential is clamped at zero (117).

Two of the groups cited (114, 119) use "bags" made from frog leg skins, stocking-like. The reader should realize that in these the ions move only by building a concentration gradient which must retard their rate of flux. Care should be exercised in interpreting rate studies made with this otherwise useful preparation.

Garby & Linderholm (121) find that aminophylline increases the ionic conductance of frog skin four times the normal. The D_2O fluxes remain unchanged. Possibly pores which ordinarily restrict the ions open up.

Isolated Tissues

Osmotic phenomena in isolated tissues.—Isolated tissues swell when soaked in artificial saline media. Ion accumulation mechanisms fail, the cell becomes permeable to salts in both directions, and, like a sievelike bag of protein, the tissue ultimately swells as a Donnan system no matter what concentration of salt (short of denaturation processes) is added to the outside. The latter fact, together with fresh tissue freezing point determinations, has led to the belief that *in vivo* osmotic pressure of tissue cells is several times higher than that of extracellular fluid [Reviewed by Bartley *et al.* (122)].

The evidence starts with Deyrup's simple observation (123) that disaccharides, not monosaccharides, are impermeant to the leaky membrane and prevent swelling at concentrations even below isosmotic. The sucrose need only counter the "colloid osmotic" pressure of the injured cell. Next comes the report of Conway & McCormack (124) that long suspected tissue decomposition lowers the freezing point depression of tissue extracts to the inordinately low values often reported. Tissue extracts prepared in the presence of the inhibitor mercuric chloride produce a freezing point depression of $-0.55°$ C. ± 0.007 S. E.[2] compared to a value for serum of $-0.55°$ C ± 0.005 S. E. Finally Wilson (125), encouraged by M. H. Jacobs, shows that mildly damaged leucocytes mimic all the properties of a protein-filled bag; swelling in 0.15 M NaCl, shrinking in 0.3 M sucrose, showing intermediate behavior in 0.05 M sucrose in 0.125 M NaCl. Tissues with fast ionic exchange systems such as kidney slices show this deterioration quickly whereas erythrocytes with very slow exchange survive in saline rather well. Deyrup (126) cites minor difficulties for this comprehensive view.

Kidney slices.—It is difficult to epitomize the results of exchange studies on incubated tissue slices. The conditions of incubation and the mathematical treatment, particularly for extracellular Na, must be extensively described. Whittam & Davies (127) fit equations to their data which are more extensive for Na^{24} than for K^{42}. Whereas Mudge [(128); see (8, 9)] discusses K^{42} exchange at greater length particularly with regard to a carrier mechanism which he feels is as specific for K as for Na.

Mitochondria.—The isolated mitochondrion shows weak accumulation of ions such as might suggest a role in ion transport [Bartley & Davies (129); Bartley, Davies & Krebs (130)]. The particles encompass a huge share of the total oxidative phosphorylations occurring within the cell and thus might be expected to contribute to the energy of transport. However, this need have no relation to their ability to accumulate Na or K within themselves. The particles might constitute the sole binding capacity for K in the cell, the cell membrane serving only as a corral to contain them. Preparation technics make computations unreliable. Spector (131) centrifuges down rat liver mitochondria at 0° C. in 0.25 M sucrose. One gm. of mitochondrial nitrogen

contains the following μM. of cation: K, 620; Na, 300; Mg, 240; Ca, 120. In this medium, 1 ml. of mitochondria contains 2 mg. of N. This would amount to 1.24 m.eq. K/l. of packed particles, even less K than in blood plasma. Stanbury & Mudge (132) relate K to nitrogen in whole liver and in mitochondria, using NaCl washing. From their data, I estimate the particles to contain one-fourth the K concentration of fresh liver. These fragmentary data do not speak for a K binding role. Actually the K binding is no stronger than that shown between certain enzymes and their metallic activators [Boyer, See (8), p. 195], but this possibility alone is worth further study. K^{42} exchanges into the incubated mitochondria so completely and rapidly that the rate cannot be timed (129).

Na binding (129) is actually stronger than K. This is the required complexing tendency of a carrier molecule for Na transport. What special orientation or movement of the mitochondria could accomplish this? At 0° C. only 80 per cent of the Na in the bodies is exchangeable, but if α-ketoglutarate is added all the Na exchanges at once at this temperature. Dianzani (133) discusses whether mitochondria possess a selective membrane. Raaflaub (134) studies swelling, and Cleland (135) times the penetration rate of K, Na, glucose, and sucrose.

Capillaries

Grim (136) indicates that Pappenheimer, Renkin & Borrero (137) are in error in applying the van't Hoff relation to their "isogravimetric" perfused cat limb which is used to measure capillary permeability. The equation describes an equilibrium condition, whereas in the isogravimetric limb the solute is continually moving across the capillary membrane as venous hydrostatic pressure is jockeyed to keep the volume of interstitial fluid (limb weight) constant. Grim quotes the correct equation taken from Laidler & Schuler (138). Pappenheimer's calculated pore area will require correction by a constant factor k, which is generally less than 1.0 but which will have a different value for each solute.

Pappenheimer's view (3, 139) is that water solubles pass by way of pores between the capillary endothelial cells and that lipid solubles pass in addition across the endothelial cells. Renkin (140) contrasts the behavior of water soluble urea against a family of oil soluble 5-pyrazolones including antipyrine. The penetrations are so fast that the exponential time course of the "osmotic transients" cannot be charted. However, the peak osmotic transients attained serve to place the compounds in a series. Compounds with higher olive oil/water partition coefficients also penetrate faster. Also lowered temperature slows the oil series more than it does urea as though the cool congeals the lipids in the cell membranes. The method of osmotic transients seems ill-adapted for use with these rapid penetrators.

Chinard (141) discusses the choice between bulk filtration and diffusion as the transfer mechanism across the glomerular membrane. On page 582 he sets a verbal trap for the filtrationists to the effect that opposing osmotic pressure cannot counter a flowing stream; that stream flow is influenced only

by hydrostatic pressure, not vapor tension, and would therefore cease only when the difference in hydrostatic pressures across the capillary wall becomes zero, which it never does. Does the steady state require a stopped stream? Chinard derives an equation by which glomerular transfer occurs by diffusion. The area required for the diffusion front at the known rate is the entire endothelial surface of the glomerulus rather than just the cross sectional area of the intercellular pores.

The plasma "disappearance curve" for isotopic electrolytes is invalid on two counts as an indicator of the turnover of ions within the capillary. The specific activity declines sharply, possibly to zero, along the course of a capillary because of the tremendous rapidity of the transcapillary exchange. Thus, arterial plasma values yield no inkling of what is the functional specific activity from point to point along a capillary. Ninety-five per cent of the intravenously injected K^{42} leaves the circulation in but three circuits around the circulatory tree [Walker & Wilde (28)]. This is less critical for slower molecules. The coup de grâce comes from Chinard & Enns (142) who delineate the "indicator dilution curves" for T1824 and D_2O as a quickly injected slug of the indicator traverses the pulmonary circulation of dogs. The dye is supposed to remain in the circulation. The peak of the D_2O curve is lower than that for T1824, and the declining right wing of the curve overrides that for the dye. Apparently the D_2O slug first leaves and then later comes back into the capillary bed again, all in one traversal. The mathematics corrects for such return flux but only on the assumption that the tag comes from a mixed extravascular pool. The curves deserve further study for what they show about the circulation as a dynamic mixing and transporting device [Walker & Wilde (28); Sheppard *et al.* (29); Turner, Ferrel & Overman (143)]. Curves for calcium (144, 145) and certain crystalloids (146) have now been described.

Chinard & Flexner [See also Fries *et al.* (147)], using their indicator dilution curve applied to several organs in the dog (148), find that parts of the slug leave the circulation in relation to the molecular weights of the molecules injected. A filter stream is supposed to carry such small molecules all together, en masse. This argues for diffusion. Pappenheimer (3), however, lets the molecules diffuse along the pore stream, with or against it. Smaller molecules get well ahead of the stream whereas large water solubles are slowed behind the stream by "molecular sieving" (139). Tissue capillaries separate dextran molecules over a critical size range so that larger plasma/lymph concentration ratios are developed for larger dextrans [Wasserman & Mayerson (149, 150)]. The renal glomerulus does likewise as revealed by inulin/dextran clearance ratios (151). These observations fit either the filtration or diffusion mechanism.

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DEVELOPMENTAL PHYSIOLOGY[1]

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Introduction

This subject is perhaps the most difficult of all those treated in these volumes, for it faces the very problem of organic form itself, not only function and its variations. Profound and elegant studies of the form-problem have recently appeared in the books of Bonner (1) and Weyl (2), while Waddington (3) has ably reviewed the epigenetics of the developing chick. There have been collective works on form edited by Whyte (4) and on growth by Boell (5). Valuable symposia dealing with biochemistry and morphogenesis have been organised by Levi (6), Miner (6a), Newth (7), and Woerdeman (8), totalling some sixty contributions. Spratt (9) has given us a notable review, while the theoretical papers of Dalcq (10), Weiss (11), and Turing (12) will

[1] Survey of the literature for this review closed in June, 1954. Although it has been found to contain a number of reports of great interest and value, the reviewer has an uneasy feeling that much useful work is going unrecorded. For example, the *Comptes Rendus* (*Doklady*) of the Moscow Academy of Sciences have appeared exclusively in Russian language since the end of World War II. About six volumes of this periodical now appear annually, containing in 1952 about 33 papers in embryology and developmental physiology, and in 1953 about 46. It is reasonable to suppose that if the Academy publishes this much itself, a good deal more would be found in other Russian-language journals. To none of these, however, does the reviewer have access, and as there are no summaries in a western language accompanying the papers, he has been unable to review them. Translations of some titles are published in *Contents Lists of Russian Periodicals*, issued monthly by the Department of Scientific and Industrial Research (Her Majesty's Stationery Office, London), but the reviewer has failed to find the names of any Russian embryologists in the author indexes of *Chemical Abstracts;* he supposes, therefore, that their works are not abstracted. *Biological Abstracts* carries the names, but more often than not the entry consists only of the translated title, without any abstract. This is a very unfortunate state of affairs. At any rate, it is interesting to see that familiar names are still appearing, such as those of L. V. Polezaiev, G. V. Lopaschov, M. I. Efimov, B. P. Tokin, and A. S. Ginzburg, together with M. I. Ragozina, A. R. Striganova, A. G. Filatova, and others. Apparently work is proceeding on skin grafts, hatching enzymes, the development of the neuro-muscular connection, the properties of blastocyst fluid and amniotic liquid, the embryology of teleost fishes, and the like. The reviewer deeply regrets that so much remains inaccessible to him and to his readers.

He also wishes to state that space-limitations have prevented more than bare allusion to a number of important fields of work. His hopes of being able to deal with the studies of the Swedish school on echinoderm morphogenesis, with carbohydrate metabolism, metamorphosis and regeneration, and the succession of energy sources, could not therefore be fulfilled in this place.

be read with interest. Others giving food for thought, though not directly concerned with animal morphogenesis and determination, are those of Castle (13) and Larner (14). At the present time developmental physiology and chemical embryology are full of vigour in most parts of the world,[1] and while many lines of work are direct continuations of those previously surveyed by the reviewer (15, 16), others are quite new adventures.

Primary Organiser Phenomena

A central place in research is still occupied by the analysis of the primary induction of the vertebrate neural axis, for on the success of this all understanding of dependent differentiation itself depends. After the first fundamental discovery that the neural inductor effect was stable to chemical denaturing agents (1932), its elucidation was thought of as a problem in a new kind of endocrinology. But great difficulties were introduced by the second fundamental discovery (1934) that in certain circumstances the inductor property could be awakened in tissues which did not normally show it, and that the ventral ectoderm (the only reactor upon which the inducing property could be tested) was one of these. Hence the concept of indirect induction [set forth at the pause during World War II (16, p. 182)]. Hence the situation that all the purified chemical substances which had been tested (and some of which had proved quite effective in neural induction) might be, and probably were, acting as indirect inductors, no light being thrown by them on the nature of the naturally occurring substances.

After the war, Holtfreter (17), while demonstrating that under conditions of normality no ventral ectoderm can ever spontaneously neuralise in culture, developed the concept of sublethal cytolysis, in which the tissue's own neural inductor would be liberated. This is still valid, inspiring such work as that of Mookerjee (18) which shows that heat shock will not do. Holtfreter also (19) defined the conditions of stability of the tissue; they happen to be those in which the yolk-platelets are stable [for new work on this see (20) and (105)]. There followed, during the past decade, a widespread tendency, especially marked among those of primarily zoological and morphological interests, to retire to that celebrated last redoubt of baffled biological thinking, the "unspecific stimulus," (cf. 21, p. 267; 22, p. 48). Holtfreter himself has sometimes seemed to approve of these proceedings (23, pp. 321, 349; 24, p. 41). Even parthenogenetic fertilisation, so often appealed to, is far from being as simple as this [cf. Shaver (25)]. We cannot put all the weight upon competence or reactivity [cf. Holtfreter (26, p. 140)], basic though its importance is, and though it also can be investigated physicochemically. In any case, those who continued to adhere to the view that a specific biochemical or biophysical stimulus passes during the induction process [cf. Raunich (27); Brachet (28)] now find that the tide has turned. Some, of course, have appreciated this more quickly than others [cf. Nieuwkoop (29)].

Elucidation has come from the study of regional specificity (the headness

or tailness of the primary organiser) combined with the use of adult tissues, often of other species, as inductors. This line of work, begun in Germany before the war by Chuang Hsiao-Hui at Holtfreter's suggestion, has led to results of great importance in Finland and Japan. In a series of papers Toivonen & Kuusi (30 to 34) established that inductions carried out in the newt by such tissues as the liver and kidney of the guinea pig, for example, were qualitatively varied. The former gives only archencephalic inductions (forebrain, eye, lens, nasal placodes, balancers), the latter only rhombencephalic inductions (mid- or hind-brain, ear-vesicles) or spinocaudal inductions (neural tubes with notochord, muscle, tails, fins, pronephros, blood, and limb-buds). Much work has been done on other tissues also, all of them being subjected to various chemical fractionations, with results not yet completely clear. What is quite clear, however, is that the very different regional effects would require as many different kinds of sublethal cytolysis if the hypothesis of specific inductor substances were to be rejected. Many findings would also be inexplicable, e.g. the steady decrease of archencephalic and increase of spinocaudal effects found by Yamada (35) on air-drying extracted muscle-proteins. Conversely, Toivonen (33) found that hunger of the donor animal progressively decreases the rhombencephalic, and increases the archencephalic effects; this has now been confirmed by Engländer *et al.* (36). The archencephalic inductor is, of course, thermostable, while the spinocaudal one (if it is only one) is thermolabile and undialysable; the most recent view of the Finnish school seems to be that the former is a low molecular-weight breakdown-product of nucleic acid while the latter is a polymerised nucleoprotein, but this is provisional (cf. 69). Engländer *et al.* (36) also find that prolonged standing in alcohol of rhombohormic and spinohormic adult tissues (if such terms may be coined) causes a loss of these properties and an appearance of the archihormic property; while tissues which are primarily archihormic from the beginning remain so. Though results with ribonuclease (cf. 106) contradict those of earlier workers, the generalisation is justified that the rhombo- and spinohormic inductors take precedence if they exist in a tissue; only upon their destruction does the archihormic property come into play. Many believe, therefore, that they are its chemical precursors. These facts gave new meaning to wartime Japanese work which had been rather overlooked, e.g. the conversion by Okada & Takaya (37) of tail-organiser into head-organiser (to use the old terms) by denaturation and ageing. On this see also Okada & Hama (37a) and Kawakami (37b).

In the past year Toivonen has made what may come to be regarded as the third fundamental experiment in this field. Stimulated by the finding of Levander (38) that an alcohol extract of adult bone can, when injected into muscle, induce there cartilage and bone cells, he found (39, 40) that alcohol-denatured bone-marrow would act in the newt as a pure mesodermal (mesohormic) inductor. After implantation, notochord, fins, limb-buds, myotomes, pronephros, mesenchyme, blood, with proctodaeal and anal openings, all appeared; but not a single characteristic neural cell, still less neural vesicles

(even unspecialised) or neural palisades or plates. Such specificity points inescapably to direct, not indirect, induction. This discovery validated the earlier work of Okada (41), who had obtained purely mesodermal inductions with newt skin, though if this was heat-denatured the archihormic property of neural induction appeared, and even rose to a maximum with duration of boiling before disappearing. We may now have to visualise, therefore, four separate inductors, regionally specific, within the primary organiser, though the view of Waddington (42) is plausible that there may be only two evocators, neural and mesodermal, mixed in various proportions. Waddington & Deuchar (43) have at any rate proved that regional differentiation depends in no way upon the length of exposure time of the competent tissue. Yet the events are very complex [Eyal-Giladi (107)].

Further explorations of nucleins as inductors were made by Brachet, Kuusi & Gothié (44, 45). RNA[1] fractions give archencephalic inductions, so also cytoplasmic microsomes. Blockage of terminal amino-groups by formol and nitrite abolishes the rhombo-hormic property while not affecting the archi-hormic [confirming Lallier (46) and Kuusi (34)], but formol may also annul competence in the adjacent reactor [Smith & Schechtman (47)]. Acetylating the amino-groups allows some rhombohormic activity to persist. Dyes believed to combine with nucleic acids have no effect upon neural (archihormic and rhombohormic) induction (48). There have been valuable new studies on the loss of competences in ectoderm during ageing (49) and on the inductions performed by successive antero-posterior levels of normal archenteron roof (50) and neural plate (51). The effects of interposition of semipermeable membranes between inductor and reactor [Brachet & de Scoeux (52)] remain enigmatic. Isotopic C^{14} migrates from the former to the latter (53) though P^{32} does not (54). Failure of the primary organiser in anidians has received renewed study (55, 56, 57).

Gastrular Metabolism

At the time of the first tactical check, when the implications of indirect induction were being realised, the Cambridge school naturally turned to an analysis of the metabolism of the amphibian gastrula in the hope of throwing light on the physiology of evocator liberation. This had become a possibility because of the ultra-micro methods developed at the Carlsberg Institute. During the past few years this line of attack has been pursued everywhere with great vigour, but the results obtained, even if some of them were not mutually contradictory, are hardly yet sufficient to give us a coherent picture of events. The problem also involves a special difficulty foreseen many years ago (cf., e.g., 15, p. 912). Since amphibian cleavage is holoblastic, every cell in the blastula and gastrula is loaded to varying degrees with

[1] The following abbreviations have been used in this chapter: RNA (ribonucleic acid); ATP (adenosinetriphosphate); DNA (desoxyribonucleic acid); an/veg (gradient from animal pole to vegetable pole); d/v (dorso-ventral).

"inert" yolk, and the investigator is thus bereft of that classical standard of all biochemical comparisons, the dry weight of the tissue.

There now exist a large number of papers reporting quantitative estimations of chemical entities and metabolic rates for different separated parts of the gastrula. As the methods used, and (at least as important) the stages taken, have differed widely, there is urgent need for a careful and detailed review of the situation. The question was taken in hand first by Boell (58) and especially by Gregg & Løvtrup (59). Using 10 mm. radial sections of a median sagittal slice, they studied the relation of a number of entities to nonyolk nitrogen as well as to total nitrogen. According to expectation, for the commencing gastrula, nonyolk N in percentage of total N showed a marked gradient decreasing from the animal pole to the vegetal pole (an/veg), and no dorso-ventral (d/v) gradient. But the paradoxical nature of the case is shown by their values for saponifiable fat. If related to total N it shows a marked an/veg gradient and a slight d/v one; if related to nonyolk N the position is reversed; there is a marked veg/an gradient and no d/v one. Barth & Sze (60) concur with the former conclusion using dry weight; it may be remarked in passing that the result is a surprise, for most workers must have tended to think that fat would be found mainly in the large white yolk-endoderm cells rather than in the animal pole ectoderm (presumptive neural plate). No d/v gradient in respiratory rate was found by Gregg & Løvtrup (59), in agreement with Boell & Needham (61), but contrary to more recent work of Ornstein & Gregg (62). Conversely, the d/v gradient in anaerobic glycolysis affirmed by earlier workers is contested by Gregg & Ornstein (63).

Many other interesting results have accumulated. Fujii *et al.* (64), referring to dry weight, found 67 per cent more adenosinetriphosphatase and 43 per cent more ATP[2] in the dorsal lip of the blastopore than in the ventral ectoderm. On the same standard, Sze (65) found for respiratory rate a marked an/veg gradient[3] and a much less marked d/v one.[2] A desire to find two gradients in agreement with the Dalcq-Pasteels theory seemed to show itself here; this should be guarded against. Then there has been a careful study of phosphoprotein phosphatase [Harris' enzyme (66)] by Metzger-Freed (67) who gives more statistical treatment than has been customary in these fields. This important enzyme shows (on dry weight) a slight veg/an gradient and no d/v one.

The biochemical problem centres round a decision as to what exactly is to be considered the best measure of the cytoplasm or "hyaloplasm" itself, if indeed that alone is to be considered "living." Barth & Sze (60) introduce the nonparticulate enzyme dipeptidase as a measure of this entity, and give its properties (an/veg and d/v). But when Sze (65) uses it as a reference for respiratory rate, it yields results just the opposite from dry weight and total N, i.e. strong veg/an instead of strong an/veg, and no d/v instead of slight d/v. When related to an extractable fraction ("non-yolk dry weight") all gradients completely disappear. Metzger-Freed (67) uses five standards of reference. We are evidently approaching a time when every chemical entity

in these holoblastic embryos will be expressed in terms of every other chemical entity. Such a relational network, which will resemble some patterns already met with in allometry, will require for its grasp a considerable intellectual effort, and it may be some time before we can see just which of the relationships will be of real significance. Yet another approach (which however will not bypass the problem of reference standards) is that of Flickinger (68), who compares the uptake of C^{14} from labelled CO_2 among the various regions of the gastrula.

Secondary Inductor Phenomena and Regulation

On dependent differentiation at stages later than that of the primary organiser a wealth of information continues to accumulate. By way of transition we may refer to the quantitative factors studied by Grobstein & Zwilling (70, 71, 72). Chick or mouse blastoderms cultured first *in vitro*, then *in vivo* as "cluster-cultures," will not individuate and produce a neural axis if in combinations less than about six one-sixteenth fragments. This almost suggests that some chemical substance is acting as a limiting factor. In clusters of mouse somites it is possible to demonstrate clearly the inducing action of neural tube in the formation of cartilage and bone [Grobstein & Parker (73)]. According to Holtzer & Detwiler, any part of the somite can be induced to form cartilage by the spinal cord (74). The dorsal part of the vertebral column is normally induced by the cord (75), and the dorsal fin by the neural crest (76). The well-known effect of Li^+ in inhibiting the differentiation of notochord has been studied by Lallier (77, 78); it substantially decreases anaerobic glycolysis and respiratory rate while leaving respiratory quotient unaffected. It also reduces cytoplasmic RNA, slows glycogen breakdown in the invaginating mesoderm, accelerates loss of ectodermal competences, exerts its action on contiguous implants, and persists in transplants, inhibiting their development in normal embryos. Notochord reduction in *Xenopus* under Li^+ has been described by Bäckström (79) and notochord overgrowth in *Rana* under SCN^- by Leone (80); this is impressive, but to the reviewer the efforts made by the Swedish and Italian schools to analogise events in echinoderm and amphibian development seem sometimes a little forced.

Before leaving the interactions of neural, muscular, and osseous cells, mention must be made of the discovery by Levi-Montalcini & Hamburger (81) of a diffusible factor emanating from sarcoma tissue which, when implanted on the chorio-allantoic membranes of the chick, brings about a great hyperplasia of the sympathetic ganglia, and hyperneurotisation of the viscera, in the body of the embryo. No nerves reach the tumour tissue itself. Breedis (262) has reported success in inducing accessory limbs in amphibia by application of chemical carcinogens, a revolutionary discovery. Interesting work on the self-differentiation of the sternum *in vitro* has been done by Ch'en Jui-Ming (82) who shows that its segmentation is due to an inductive effect from the ribs. On morphogenesis *in vitro* in general, see the excellent review of Fell (83).

Closer study of secondary inductions such as that of the lens by the eye-cup may afford another way of escape from the dilemma of indirect induction, since it has never been shown that denatured presumptive lens ectoderm can stimulate other ectoderm to the production of lenses [cf. Kawakami (84)]. The same may be said of gill induction (85). We now have a first study on the determination of the atrophy of a vestigial organ, the duct of Müller in male bird embryos (86); and total agenesis of external sex organs has been described (87). Hadorn has reported further (88) on his important work on regulation within the field districts of insect imaginal discs.

As has long been known, inductive phenomena occur during the later development of mosaic eggs. The functions of the polar lobe in *Ilyanassa* have been followed by Clement (89), while Berg & Kutsky (90) have provided a pioneer study of the metabolism of the polar lobe in *Mytilus*. These cells can now be had in bulk (151), and it has been found that peptidases are not involved in the plasm segregations (150). Elaborate work on the differentiation of *Limnaea* embryos by Raven and his colleagues (91 to 103) has also been reviewed by him (104).

Proteins and Amino Acids

The most important feature of organ and tissue differentiation at the purely biochemical level is no doubt the synthesis of specific proteins. While the study of embryonic development is assuredly an end in itself, it seems likely to throw rapidly increasing light on the biosynthesis of proteins in general, whether this is a stepwise coupling of peptides, or simultaneous pattern formation on templates [cf. Campbell & Work (108)]. One essential preliminary is a full understanding of the reserve proteins of the egg, towards which there has been some advance, especially concerning the ovomucoids and ovomucins (109 to 113). But greater metabolic interest attaches to such studies as those of Rudnick, Mela & Waelsch (114) who find that as late as the sixth day of incubation 95 per cent of the glutamo-transferase activity is in the yolk-sac, and not until the thirteenth does the embryo overtake its membranes in this respect. Such work is of great significance because of the probable role of the glutamic radical cycle and of transpeptidisation in protein synthesis (115, 116). It raises the question whether the elaboration of specific tissue proteins may not go on in locations far removed from the sites which they will ultimately occupy. The distribution and activity of similar enzymes will be followed with attention (cf. 117, 118, 119).

Another, related, problem is that of ascertaining whether embryonic cells must accept only amino acids, or whether they can incorporate suitable proteins ready-made. Some time ago Weiss & Wang (120) claimed that incorporation of embryonic organ fragments on to the blastoderm brought about first a decrease and then an increase of the homologous tissue of the host embryo. This has now been strikingly substantiated by Ebert (121), who shows that while the effect is species-specific, a spleen so stimulated exceeds its control in weight and total nitrogen by 300 per cent. Methionine labelled with S^{35} is transferred from graft to host selectively, and as much as 15 per cent of

the host's spleen tissue protein apparently comes directly from the graft without intermediary hydrolysis. Francis & Winnick, too (122), using C^{14}-labelled embryo extract, assert that cultured embryonic heart fibroblasts utilise the proteins without any breakdown to amino acids.

A prerequisite of all further progress is a thorough knowledge of the movements of amino acids, whether in free, peptide, or protein form, in eggs and embryos (and their parts) during normal development. A beginning was made some years ago by Holtfreter, Koszalka & Miller (123) who concluded that no perceptible differences exist between different germ layers or at different developmental stages; but it was soon shown that this conclusion was much too pessimistic, and there set in an era of passionate paper chromatography and microbiological assay. The problem now is not to detect changes and differences, but to know which of them are really repeatable and significant. For amphibian development a coherent picture is developing; Kutsky *et al.* (124) and Ch'en & Rickenbacker (125) could group the aminoacids into different fractions rising, falling, and migrating. For the echinoderm embryo the earlier work of Gustafson & Hjelte (126) and Kavanau (127) gave similar rather plausible data, adding variations produced by Li^+; but the later results of the last-named (128) and the extraction of a bacterial growth-factor from developing sea urchin embryos (129) show rather violent fluctuations which are "believed to represent alternate periods of yolk degradation and synthesis of proteins." The sceptical may need a good deal of methodological and statistical convincing. Lundblad (130) brings forward complementary work on echinoderm embryo proteases. Work with modern micro-methods on the free amino acids of the chick embryo yolk has also been started [Williams *et al.* (131)] and will be watched with interest; nor is the silkworm being forgotten (132, 133). On problems more specific, we have work on the chick embryo's biosynthesis of niacin (134) and of vitamin B_T (135), and on nitrogenous constituents of the blood of larval urodeles (136).

An interesting, though still rather obscure, subject is that of the structure-proteins analogous to myosin which have long been found in non-muscular (and embryonic) tissues (see 137 to 140). They are often considered mainly nucleoproteins (141, 142, 143). The school of Ranzi (144, 145) continues work on the effects of ions such as Li^+ and SCN^- on their viscosity, attempting to throw light on the echinoderm double gradient thereby, (cf. 146, 147, 148). Meanwhile Cigada (149) has completed a study following the relative amounts of the two classical structure-proteins and the soluble proteins during avian, amphibian, and echinoderm development.

The Serological Approach

The methods of serology and immunology detect very small differences in protein specificities. Moreover, the rapid formation of the highly specific antibody in response to the injected antigen presents a problem of protein synthesis which the chemical embryologist can hardly afford to neglect, as appears from the stimulating review of Haurowitz (153). Not surprising was

it, therefore, that the categorisation of the antigens present in developing embryonic tissues at successive stages was attempted early in the current century (cf. 15, pp. 1444 ff.; 16, p. 30); but the procedures were so crude and the results so conflicting that the interest and imagination of embryologists was not kindled until the striking recent discovery of ten Cate & van Doorenmaalen (154) that the specific protein of the lens of the eye is detectable in the chick embryo before the closure of the lens-vesicle and before the least sign of histogenesis. In amphibia, the lens-protein could be detected at a time when the lens rudiment is nothing but a thickening of the ectoderm under the influence of the eye-cup. Does chemical differentiation always precede histological? Woerdeman (155) descries vistas of a resurrection of preformationism. He also reports (156) an experiment which, if confirmed, would be of outstanding importance, namely that while neither presumptive lens ectoderm nor the eye-cup tissue (at a stage earlier than that just referred to) shows evidence of lens-protein, their saline extracts mixed and incubated do so. Moreover (155), the iris, from which the lens is produced in Wolffian regeneration, has the property of synthesising lens-protein when cultured *in vitro*. Meanwhile, by way of background knowledge, Zuidweg (157) reports quantitative estimations of α-crystallin in early chick embryos.

It is clear that application of serological methods to the problems of experimental morphology is going to be of much value. Evidence has been accumulating that the presence of anti-sera for specific organ or tissue proteins has a deleterious effect upon the differentiation of the corresponding morphological entity [Ebert (158)]. Growing embryonic tissues are apparently able, strange though it seems at first sight, to incorporate within their cells whole heterologous proteins [Langman (159)]. The significance of this *in vitro* effect for the study of heteroplastic transplantation is obvious. It is possible to show that in interspecific hybrid echinoderm embryos (whether lethal or not) paternal antigens appear by the late blastula stage which did not enter with the sperm and which therefore betray the activity of the paternal nucleus (160). Again we see that a chemical difference can be shown to exist before any perceptible morphological difference. At specific stages, such as gastrulation in the sea urchin, new antigens appear (161), and this kind of work is now going on along a broad front for amphibia (162 to 166) and for birds (167, 168, 169, 171). Perhaps less fundamental, but still interesting, is the problem of the antibody environment of the mammalian embryo, on which there is a new book (170).

Enzymes and Adaptive Enzymes

Among those highly specific proteins which embryonic cells elaborate, the enzymes (which may not all necessarily be distinct from structure-proteins) take foremost place. Just as the embryologist must watch the parallel between his syntheses and those of antibody formation, so the new and expanding study of "adaptive" enzymes, produced by cells as their response to new substrates, must not be foreign to him. The implications of this have

been brought out by Spiegelman (172) who suggests a theory of transplant behaviour, that corner-stone of experimental morphology. Selfwise or determined differentiation would imply an incapacity of the cells to synthesize new enzymes appropriate to their new environment, while neighbourwise or undetermined differentiation would imply that they were able to react to the substrate molecules of their new environment by the formation of the necessary enzymes. This invites experimental test. Moreover, the characteristic patterns of enzymic equipment which develop in the various tissues as histogenesis proceeds (the term "enzyme-profiles" is suggested for them) may well come into being as responses to substrate stimuli acting from one part of the embryo upon another. It is of much interest that by common consent (173) the workers in the adaptive enzyme field have adopted a terminology modelled on that of experimental embryology. Some enzymes are "constitutive" (see 174), but others may be "induced" if the cell is competent so to react.

There was some hesitation in transferring to the higher animals a concept developed for microorganisms, but Knox (175) seems to have been the first to demonstrate (for rat liver nonmitochondrial tryptophan peroxidase) that they behave in the same way. Biochemists are now in hot pursuit of the protein synthesis mechanisms involved, (cf. 176, 177, 178). That enzymes can be induced in the chick embryo has been found by Gordon & Roder (179), who injected adenosine at successive time-intervals into the egg, having established the normal growth-curve of adenosine-deaminase. Repeated injection of small doses will more than double the enzyme content of the embryo. Demonstration of the induction of an enzyme which the embryo never normally possesses, however, is still awaited. The technique of injection into the developing egg is old, but it was customary to think of precursors and to look for end-products rather than for enzymes. So Ogino (180) obtained increased ascorbic acid synthesis from glucose and mannose, while the onset of protein breakdown could not be postponed by injecting monosaccharides (15, p. 998).

For individual enzymes the most important paper is one on amphibian embryo phosphoprotein phosphatase (67) which rises to a peak at gastrulation before declining, like lipase (181). Alkaline phosphatase has been less popular of late (182, 183, 184), but hatching enzymes retain interest (130, 152).

Nuclear Embryology

Whatever may be the relations between chromosomes and enzymes it is sure that the mechanisms of development will not be elucidated without knowledge of the nuclei and what they do. This field has seen some brilliant technical achievements and a steady growth of quantitative knowledge. It is now thought that during cleavage the chromosomes release what Swann & Mitchison (185, 186) call "structural agents," causing cyclical changes in birefringence and 11 other variables. Concomitant respiratory rhythms seem to be often, but not always present (263). By the use of an oxidising agent followed by a detergent, Mazia & Dan (187) have succeeded in obtain-

ing the mitotic apparatus (asters and spindles) of echinoderm eggs as one complex isolated in bulk. Starfish egg nucleoli have been similarly isolated and studied [Vincent (188)].

New techniques have made possible the transplantation of nuclei from one cell to another with comparative ease. Briggs & King (189) took animal-pole cell nuclei from amphibian anuran blastulae and gastrulae and transplanted them back to enucleated eggs. The normal development of these reaffirmed the classical doctrine that nuclei do not themselves differentiate. Success with gastrula nuclei was less frequent than with those from the blastula, however, and Waddington & Pantelouris (190), working with a urodele, could not rear any of the operated embryos through gastrulation. The remarkable results of Lorch & Danielli (191) with nuclear transplantation in amoebae, nevertheless, show what promise the method holds. Another related experiment consists in injecting DNA^2 from the same or related species into the eggs, or letting them develop in sea-water containing it [Hörstadius, Lorch & Chargaff (192)]. In many conditions, heterologous DNA arrested development.

The chemical structure of nucleic acids from different sources (including eggs) has been compared by Elson & Chargaff (193). Further work has been done on the DNA content of nuclei during mitosis by histophotometric methods of the Pasteels-Lison type (194, 195, 196), but some doubt has been thrown on their validity (197). Strictly chemical estimations, however, are also subject to argument. For the echinoderm egg, Marshak & Marshak (198) criticise the figures given by their predecessors (199, 200) as being too high, yet they agree with them that at the time of fertilisation most of the DNA is in the cytoplasm. It seems to be accepted that a strong synthesis of DNA sets in at the time of the late blastula. According to Scarano & Kalckar(201) the use of C^{14}-labelled glycine and adenine shows that the former is used before the latter, and that DNA and RNA incorporate these building-stones unequally. Close correlation between DNA synthesis and rise of respiratory rate is reported for the sea urchin embryo by Comita & Whiteley (202), but such an exact proportion does not hold for mammalian liver cells throughout life (203).

Regarding amphibia, reference has already been made to the finding(25) that the "cleavage-initiating substance" in parthenogenesis is the cytoplasmic RNA granule. During growth of the oocyte, RNA synthesis is at first very active, but there is an overall percentage decline (204). Takata (205) has an interesting study of RNA distribution in the gastrula; on the total nitrogen, ectoderm exceeds mesoderm, and there is an increase at gastrulation in most regions, including the invaginating mesoderm. This would have been expected to show a decrease, following some of Brachet's well-known observations and hypotheses. A study of DNA in relation to nuclear and cell size has been made by Sze (206); while the amount in each embryo rises by synthesis, that in each cell falls enormously during development. This is a modern formulation of the classical nucleo-cytoplasmic ratio. In Wolffian regeneration, the lens (unlike the normal adult lens) is full of RNA (207).

Attention has been paid to DNA and RNA synthesis in the chick embryo by Novikov & Potter (208) and Reddy *et al.* (209). The results are so far concordant as to show a peak of both nucleins on the thirteenth to the fifteenth day of incubation, which is compared with the approximately simultaneous peak of protein content of the embryonic body (15, p. 914, 923). Isotope experiments concur that nuclein turnover is here maximal (261). This is also the optimum period for extraction of the growth-promoting factor. But it is not the period of most rapid over-all growth or protein accumulation. There have also been studies of the incorporation of C^{14}-formate into the nuclein bases of normal and x-irradiated chick embryos (210), of their cells *in vitro* (211), and of their membranes (212). See lastly a contribution on placental ribonuclease in man (213).

Experiments with Isotopes

Tracer experiments have already been referred to in several connections. What has been said, however, by no means exhausts the uses of such methods, even if it still remains the case (as was concluded at a Copenhagen conference before the last war) that they help the problems of metabolism much more than those of morphogenesis. The way in which they necessitate a revision of our ideas is particularly well seen in the following case. As a recent review (247) has pointed out, it was always formerly assumed that a fall of some analytically identifiable substance (such as triglyceride fat) during the development of a cleidoic egg implied the utilisation of this substance in metabolism. Similarly, a rise (such as occurs for ascorbic acid) implied a synthesis; and when some substance neither decreased nor increased during the period, it was natural to suppose that it did not participate in metabolism. Such was the case of cholesterol in the hen's egg. But now the use of compounds labelled with C^{14} has shown that the embryo engages in a continual destruction and synthesis of cholesterol, the average amount remaining constant. After injection of labelled acetate, Stokes, Fish & Hickey (214) found two maxima of labelled cholesterol, one at 18 and one at 168 hr. subsequently, from which it is concluded that part of the acetate is built up directly into the steroid molecule, while part is used for the formation of fatty acid chains destined for later conversion to steroid. The extra-embryonic membranes were much more active than the embryo itself, again suggesting that the role of these structures in biosyntheses has been undervalued in the past.

P^{32}, injected into developing hen's eggs, enters all components save shell and white, but it is not incorporated into the yolk phospholipins; hence the embryo, as has long been suspected, makes its own *de novo* [Webster & Ward (215)]. The proteins and glycerol of the yolk, however, can be labelled by C^{14} given as acetate to the laying hen (216). Labelled bicarbonate injected into the vitelline veins of the embryo is quickly converted to malate (217), S^{35} goes to taurine (218) and to sulpho-mucopolysaccharides (219), Zn^{65} to vitellin (220), interesting as precursor of the zinc protein carbonic anhydrase. The uptake of isotopic C and N by the sea urchin embryo has also been studied (221).

Chemical Differentiation in Organs and Tissues

As Herrmann has pointed out in a useful review (222), it is only within comparatively recent years that methods have become sufficiently delicate to permit of the following of events in one particular organ or tissue of the developing embryo. Chick muscle has been examined in a series of careful papers by Robinson (223). Before hatching, the sarcoplasmic proteins greatly decrease in relative amount while the collagen and residual proteins rise. The fibrillar protein fraction increases to just about the same extent as the nucleoprotein fraction falls, and, after hatching, this proportionate growth of the fibril proteins continues. Tropomyosin is never prominent, and it is probably not a precursor of myosin. At the earliest stages studied all the adenosinetriphosphatase was sarcoplasmic, but as development proceeds this steadily decreases in amount, while myofibrillar adenosinetriphosphatase steadily increases. The activity of the latter rises to a marked peak towards the end of incubation. On myosin in very early heart muscle, see Ebert (224).

The development of limb- and wing-buds of chick embryos has been studied by Nowinski & Yushok (225). There are differences in the relative growth-rates of DNA as between the two rudiments, though the amount of the nuclein in relation to the number of nuclei remains constant. The respiratory rates were equal, but the limb-buds showed a higher anaerobic glycolysis (if referred to DNA content, not to dry weight). There is evidently much to be discovered along these lines.

Flexner, Belknap & Flexner (226) have continued the work of their group by tracing the growth of cytochrome-oxidase, succinic dehydrogenase, and succinoxidase, in the cerebral cortex and liver of the developing guinea pig. They desire to establish the existence of a critical point for nerve development between the forty-first and forty-fifth day, and indeed the amount of these enzymes does rise rapidly from that point, but it is not clear why a critical point is denied to the liver at a later stage, where at least two of the enzymes take an even sharper upward turn. Embryonic blood is studied by Schjeide & Deutsch (227); the relative amounts of the various proteins differ widely from the adult distribution, and there are protein components which are not found in the adult.

Affinities and Disaggregations

A new epoch in experimental morphology was inaugurated in 1939 and 1944 by Holtfreter when he showed that amphibian embryonic cells could be disaggregated and reaggregated at will and that particular tissues, combined together in explants in any desired way, would manifest marked affinities or repulsions. After disaggregation of presumptive pronephros tissue, determination persisted and recombination was followed by normal development. Much is now being done in this field, disaggregation being effected by such agents as alkali, trypsin, hyaluronidase, low Ca^{++} and Mg^{++} levels, etc. Moore (228) works on echinoderms; Mookerjee (229) and Moscona & Mos-

cona (230) on the chick embryo (of the latter, limb-bud cells reassociate to give chondrogenic blastemas, and mesonephros to produce tubules).

Such methods can be used for many purposes, e.g. for studying effects on respiration, as in the work of Tipton & St. Amand (231) on neuroblast populations from grasshopper embryos, but the possibilities of analysing morphogenesis are at least as attractive. Not only can the retained differentiation potencies be examined (232), but also such properties as those of regionality (233). Thus Deuchar showed that while the complete primary organiser, even of a late gastrula, can differentiate normally itself after disaggregation and induce neural tissue, there is a loss of specific antero-posterior (archihormic and rhombohormic) properties. Particularly interesting are experiments of Grobstein (234) who dissociated the germ-layers of organ-rudiments in the mouse, then replaced them in different combinations. Thus characteristic differentiation of submandibular epithelium into branching tubules is obtained when it is combined with its own mesoderm, but not with mesoderm from other organs. Then only a thin sheet of cells is formed. Denatured mesoderm prevents spreading but does not stimulate morphogenesis; mesoderm previously cultured alone, or fully disaggregated, gives a less marked effect than full induction. The inductor will pass through interposed filters. Metanephric mesenchyme will itself form tubules under the influence of neural tissue separated from it by a filter.

These tissue interactions certainly have a close connection with affinity effects—attraction, adhesion, fusion, separation, repulsion—which are being studied by Amprino (235), and Abercrombie & Heaysman (236). These will need the attention of surface chemists. The first work on the biochemistry of combined explants has now appeared in a fundamental, if preliminary, paper by Gregg & Ornstein (237). Four movements [(*a*) endoderm embedding itself in endoderm, (*b*) mesoderm stretching in endoderm, (*c*) ectoderm spreading on endoderm, and (*d*) mesoderm fusing with ectoderm on endoderm] were subjected to the action of certain agents [anaerobiosis, uncouplers like dinitrophenol and azide, compounds blocking –SH groups, and narcotics such as 5,5-diethyl barbituric acid (Barbital)]. Space does not permit the tabulation of the findings, but this may easily be done from the descriptions given, and in general it may be said that the uncouplers had little effect on any process [except (*b*) and (*c*)], while the narcotics affected most of them [except (*d*)]. Blocking –SH groups entirely inhibited (*b*) and (*c*). The subject of fusion or refusal to fuse has been further followed by Chiakulas (238) who remarks that "the formation of stereochemical bonds between molecules at the surfaces of adjacent cells can explain the basis of cell affinity." What vistas this opens up may be conceived from the renewed attack of Mikami *et al.* (239) on *situs inversus viscerum*, which they could produce by re-implantation of notochord or prechordal plate in reversed orientation.

As a contribution to further test of some old well-known ideas Weiss & Andres (240, 241) have injected disaggregated embryonic cells (tagged by pigmentation potency) into other embryos. Tissues suffer invasion and colon-

isation, and some teratomas are formed. Rubbel, too (242), has taken up gain the fate of embryonic cells introduced into the adult body, following the testamentary paper of Spemann (243), which has perhaps been rather overlooked. Witschi (244) has dealt anew with over-ripeness as a cause of twinning and teratogenesis. The reviewer continues to believe in the importance of experimental morphology for the elucidation of the cancer problem, and he doubts not that this opinion will eventually commend itself to those responsible for the planning of cancer research.

For more than half a century advantage has been taken of the fact that since amphibian embryonic cells are provided with ample stores of yolk, explantation *in vitro* is easy. Now, however, the first successful steps have been taken towards the cultivation of avian embryonic tissues in synthetic medium [Wolff *et al.* (245)]. With gonads, syrinx, and tibia, growth in total nitrogen occurred, accompanied by considerable differentiation. Addition of *p*-aminobenzoic acid seems particularly important (246).

Developmental Block

Specific inhibition has an irresistible attraction for the mind of the investigator of organic processes; malfunction always promises to throw light on function. Hence the wide interest aroused in recent years by the failure of certain hybrid amphibian embryos and also andro-merogons to complete the gastrulation process. Often the dorsal lip of the blastopore forms but is immobilised, and both competence and inductive power of the appropriate regions is greatly reduced [Moore & Moore (248)]. Lethal hybrid nuclei transplanted back from blastula or gastrula to enucleated eggs will bring them successfully through the cleavage stages but will fail again at gastrulation [King & Briggs (249)]. The lethality of tissues arising from these embryos which die at gastrulation or tail-bud stages may be "nonautonomous" or "autonomous," i.e., it may be possible to save the tissue by grafting it into a normal embryo or it may not [cf. the review of Baltzer (250)].

Biochemical investigation has crystallised in a couple of graphs which will no doubt become as familiar as the U-shaped curve of insect metamorphosis. They are complementary to each other; on the one hand we see for the normal embryo a rising curve, on the other a falling one, but in both graphs the curve for the lethal hybrid or merogon levels to a static condition at the time when the developmental block sets in. The former of these situations is represented by respiratory rate [Ch'en (251), Sze (252), confirming earlier work by the Columbia school], RNA synthesis (253), and DNA synthesis (254). When the inhibition of respiration arrives, all the gastrular regions are equally affected (252). The latter of the two situations is represented by glycogen utilisation (255) and by the disappearance of free purine bases (256) which normally enter in to the synthesis of the nucleins.

It has moreover proved possible to imitate in some measure the developmental block at gastrulation by thermal shock both in amphibia (257) and birds (258), by high oxygen pressures (259), and by uncoupling

agents such as dinitrophenol and usnic acid (260). Some of these conditions prevent the continued synthesis of RNA just as in the case of the blocked hybrid (253, 260).

Dissection of Morphogenesis by Metabolic Analogues

If foreign genes thus prevent the utilisation of the embryo's substrates by its enzymes, a parallel at once presents itself with the actions of "metabolic analogues." A flourishing trend of research is now under way which aims to achieve a causal morphology by detecting the association of specific developmental failures with specific interferences. A single substance is presented to the embryo's metabolic machinery, nonutilisable but closely similar in structure to one or another vitamin or building-stone molecule; competitive inhibition then throws a particular enzyme system out of gear, with all that may imply if indeed it is the limiting factor for a particular morphogenetic process. Agents available in the past were very unspecific (cf. 15, pp. 1420 ff.) and efforts to give biochemical meaning to their actions generally had to be renounced; it now remains to be seen whether the analogues [cf. the review of Woolley (266)] will really raise the method to a higher plane.

During the past couple of years a variety of species of embryos have been tested with analogues of amino acids (264, 265), unnatural synthetic cytosine nucleosides (267), substituted purine and pyrimidine bases (268), folic acid analogues (269, 270), nicotinic acid analogues (271), and thiamine analogues (272). Cravens (273) has contributed a partial review. Among the anomalies observed after administration of the substances have been abnormal central nervous system differentiation, failure of the somites to separate from one another, inhibition of growth in length, oedema, distention of amnion and allantois, greatly reduced vascularisation of the extra-embryonic membranes, deformations of the limb-buds, etc. It will be for future work to sort out the numerous effects and to establish the specificity of their occurrence. But there seems reason for a certain optimism; for example (268) it is found that those purine and pyrimidine analogues which bring the development of the amphibian neurula to a stop are precisely those which antagonise folic acid or the *Leuconostoc citrovorum* factor in microbiological systems.

This subject obviously has rather wide ramifications. For instance, the morphogenetic effects produced by an analogue of a vitamin will have to be carefully compared with the effects of its absence, hence the interest of the recent review of Giroud (274) on avitaminosis malformations. They also invite comparison with those produced by lethal or semilethal genes, effects which, as has long been realised, are extraordinarily specific [see the recent review of Glücksohn-Waelsch (275)]. Indeed, the analogues may well turn out to produce phenocopies of lethals already known. Karli's study (276) shows how the genetic suppression of visual cells in the rodent retina can be reproduced by iodoacetate. If pilocarpine can give rise to rumplessness and syndactylism in chick embryos which are not genetically condemned to these defects (277), it may well be because of an interference with nicotinic acid metabolism (278). Landauer has also found (279) that boric acid [which in

Drosophila induces many phenocopies (280)] causes in chick embryos extreme mandibular shortening, facial coloboma, absence of digital appendages, and shortening or bending of the tarso-metatarsus—all anomalies pointing to interference with the riboflavin supply. Lastly, it remains to be seen to what extent the interesting groups of radiomimetic compounds, and of mitotic inhibitors of different kinds, act by preventing the function of normal enzyme systems, or more directly on the properties of structure proteins.

PROSPECT

It is tempting to condense into the shortest possible compass a statement of how the past and present of developmental physiology look from the focal point of the present time. Ultra-micro methods at the level of the individual blastomere, and hitherto unimagined techniques of isolating cell component structures, are making almost everything possible. We may therefore expect to obtain at last, during the coming few years, a coherent picture of the metabolism of the amphibian gastrula, and the connection (still an open question) between the double gradient of the echinoderm embryo and its chemistry continues to offer fascinating possibilities. Progress can and will be made in the identification of the naturally occurring substances which mediate the stimuli of morphogenetic inductions in vertebrates. Protein chemistry, moreover, seems capable of furnishing explanations for what we know as reactive competence. It will be necessary to learn from all fields where rapid protein synthesis is under study, from immunology and from microbiology. It looks as if several time-honoured conceptions are due for revision, e.g. the idea that an embryo can lay down lipoid molecules ready made, and the converse idea that it can only accept free amino acids; or, again, the idea that in a cleidoic egg constancy means nonparticipation in metabolism. Techniques now developed for the disaggregation of embryonic tissues into their constituent cells lay open for solution the problem of just what morphogenetic properties cells can retain during isolation. The combination of embryonic tissues in all desired variations, now possible, will permit of a real physiological analysis of the "cell stream" movements, in which the help of the surface chemist is beginning to be an urgent need. Finally, much is to be hoped from a systematic attempt to identify the limiting biochemical factors in individual morphogenetic processes by the study of effects produced by analogue molecules. This will link up with knowledge of the physiological mechanisms of lethal genes, foreign genes, and avitaminoses. Another col has been reached on the Mount Everest of organic form.

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THE PHYSIOLOGY OF CONNECTIVE TISSUE[1,2,3]

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Most connective tissues of the adult are derived from mesenchyme and consist of ground substance, fibers, and the connective tissue cell or fibroblast. In order to satisfy the varied functional requirements of the body, these components become modified in quantity, composition, or arrangement. Thus, are provided the following special varieties of connective tissue: mucoid, reticular, adipose, elastic, regular, cartilage, and bone. This review is concerned primarily with regular or fibroelastic connective tissue, although it is not always demarcated sharply from the other types. In addition to its essential components, fibroelastic connective tissue contains mast cells, plasma cells, macrophages, and some white blood cells. The fibers are reticular, collagenous, and elastic in type. Fibroelastic connective tissue forms the supporting framework for blood vessels and constitutes with them a system to provide for interchange of substances between the blood stream and other tissues. Inflammation involves alteration of both blood vessels and connective tissue.

Normal Connective Tissue

Cells.—The cytoplasm of fibroblasts contains acid phosphatase (146) and, during proliferation, small amounts of glycogen (21). As determined by reference to the constant amount of desoxyribonucleic acid phosphorus which is present in the nucleus of somatic cells, protein nitrogen and lipid phosphorus increase during the early phase of intense cellular proliferation in fibroblast cultures. Later an increase occurs in ribonucleic acid phosphorus and acid-soluble phosphorus (51). Radioactivity is present in mesenchymal cells after administration of bicarbonate-C^{14} to newborn rats (82). Fibroblasts carry out transaminations since addition of glucose-C^{14} to the supporting medium of cultures leads to the appearance of radioactivity in several nonessential amino acids of the tissue protein (66).

Many factors condition the growth of fibroblasts *in vitro*. An 80 to 90 per

[1] This review was written as a supplement to that of Ragan (166) and covers the literature for the period of June, 1951 to June, 1954. Limitation in space required that only a few of the hundreds of worthy papers be cited.

[2] The following abbreviations have been used in this chapter: RNA (ribonucleic acid); PAS (periodic acid-Schiff reagent; DNA (desoxyribonucleic acid); DCA (dexoxycorticosterone acetate); DOC (desoxycorticosterone); 48/80 (a product of condensation of *p*-methoxy-phenyl-ethyl-methylamine with formaldehyde).

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cent reduction in mitotic activity occurs when they are grown in a medium from which amino acids have been removed by prior rapid dialysis. Replacement individually of arginine, histidine, lysine, glutamic acid, aspartic acid, methionine, or tryptophan stimulates cellular division. Cystine and proline are ineffective. When all of these amino acids are replaced in combination, the effect on growth is determined by their relative concentration (110). Fibroblasts utilize glucose, mannose, or fructose (89). The growth-promoting action of embryonic extract is related to its nucleoprotein fraction (113), mitochrondria, microsomes, and dialyzed soluble cell fraction (114).

The *in vitro* suppression of fibroblastic proliferation by heparin may be a result of interference with the metabolism of nucleoproteins since RNA^3 accumulates in the cytoplasm of fibroblasts affected by it (152). The capacity of tetrasodium 2-methyl-1:4-naphthohydroquinone diphosphate and related compounds to inhibit mitosis is correlated with the degree of their phosphorylation. These effects are summated with those induced by concurrent x-irradiation (139). Histidine counteracts the inhibiting effect of cobalt (143).

Observations on the mast cell are conflicting because many investigators have failed to recognize the unique cytological characteristics of the cell. It is exceedingly fragile; dispersion and clumping of granules and cytoplasmic vacuolation occur commonly in most fixed preparations. These variations are not observed *in vivo* (55). Mast cells vary considerably in staining reaction and form (141) as well as in the number found in different areas of the same animal and in different species. Hence, counting of the cells is usually required to determine changes in number and cytological studies must be controlled with unusual care.

The granules of mast cells contain disulphide groups (22) and are metachromatic (46, 69) because of the probable presence of heparin monosulphuric acid (208). Surrounding the metachromatic core is a material which stains with Sudan black B and contains alkaline and acid phosphatase (208). Serum ultrafiltrate maintains the granulation of cells grown *in vitro* (211). Intraperitoneally administered S^{35} is concentrated in mast cells (7). Aggregation of the granules follows total body x-irradiation (107).

Three functions are attributed to the mast cells: (*a*) storage of histamine, and the secretion of precursors of (*b*) hyaluronic acid and (*c*) of heparin. Fluorescence is localized in mast cells after the injection into rats of fluorescent histamine liberators. They are reported to undergo vacuolation and disruption under the influence of these compounds (144, 170), concurrently with an increased liberation of histamine (64). Disruption of mast cells with $48/80^2$ also is denied (55). Prior treatment of rats with antihistaminic drugs does not impede their uptake of fluorescent histamine liberators (170). An impressive correlation exists between the concentration of mast cells and the histamine content of a tissue (171). Refractoriness develops toward repeated injection of 48/80 because of a lack of labile histamine (188). However, tissue mast cells are not the only source of histamine, because its release from blood cells can be induced *in vitro* (103).

The hypothesis (5) that mast cells secrete the hyaluronic acid of the

ground substance is not well-supported by available evidence. The correlation between the number of mast cells in a tissue and the quantity of ground substance under varied experimental and pathological conditions is exceedingly poor. The failure of prior digestion of mast cells with hyaluronidase to destroy their metachromasia demonstrates that the stained material is not hyaluronic acid (46). On the contrary, many observations indicate that ground substance is produced by the fibroblast or its mesenchymal cell precursor. Granules containing glycoprotein occur in fibroblasts (77) and in the mesenchymal cells of embryos (123). Ground substance is laid down in the embryo, granulation tissue, the cock's comb (121), and sex skin of the monkey (58) in the neighborhood of mesenchymal cells or fibroblasts at a time when mast cells are exceedingly sparse or exhibit no cytological modification. The abundant ground substance of the human umbilical cord is associated with both mast cells and mesenchymal cells which contain metachromatic granules (192). Other possible cellular and noncellular origins for ground substance still merit consideration. The observation (96) that mast cells degranulate during release of heparin in peptone shock is not confirmed (11).

The reticuloendothelial system includes the macrophages of fibroelastic connective tissue and phagocytic cells of many other tissues. Administration of choline increases the rate of phagocytosis of $CrP^{32}O_4$ in mice by 100 per cent (93). Investigation of phagocytosis by observing clearance of India ink from the blood is hazardous if commercial preparations are used at high doses. The shellac and other blood-clotting substances which they contain cause microcoagulation of fibrin and thereby modify the clearance of carbon (86). ThO_2 (Thorotrast) is taken up most rapidly by the liver and spleen. Some is carried in macrophages to the lungs (59). Within 10 days most of the ThO_2 is eliminated in the urine and feces. It reaches the intestinal tract by way of the bile and the swallowed respiratory secretions containing ThO_2-laden macrophages (84).

The behavior of phagocytes is modified by the nature of mineral particles which they ingest (164). Total body x-irradiation interferes with phagocytosis only at high dosage or under special conditions (72, 195). The relationship of reticular connective tissue cells to neoplasia is reviewed (57). Microscopic (140) and immunologic (61) evidence indicates that plasma cells store antibody.

Ground substance.—Ground substance consists of mucopolysaccharides, water, salts, proteins, and other substances. Bovine cornea yields chondroitin sulphuric acid, a component resembling hyaluronic acid and a sulphated mucopolysaccharide. The latter, designated as keratosulphate, makes up half of the total mucopolysaccharide content and is the only known sulphated polysaccharide of animal origin which does not contain a uronic acid (134). Corneal mucopolysaccharide readily forms stable complexes with protein (209). The hyaluronic acid of ox synovial fluid exists in an easily degraded complex containing 25 per cent protein (147).

The structure of hyaluronic acid is not established (135) but appears to

be an unbranched polymer formed alternately from D-glucuronic acid and N-acetyl-D-glucosamine with a pyranose configuration and beta-linkages in positions 1 and 3 between glucosamine and glucuronic units (101). Group A streptococci synthesize hyaluronic acid by direct conversion of glucose in the medium to the glucuronic acid and glucosamine moieties. The N-acetyl group appears to arise from, or be in equilibrium with acetate in the medium, this being derived only in part from glucose (178). In the body, hyaluronic acid is synthesized more rapidly than chondroitin sulphuric acid (180). Sodium sulphate-S^{35} is taken up rapidly by connective tissue and probably is incorporated chiefly into sulphated polysaccharides (29).

Purified hyaluronic acid does not stain with periodic acid-Schiff reagent (52) and, in the sol state, is non-metachromatic. As a gel or dry film it exhibits a metachromasia which is less stable than that of sulphated polysaccharides. The extent to which hyaluronic acid contributes to metachromasia of ground substance is unknown (194). This reaction is modified by many factors (177). The postulation that purified testicular hyaluronidase preparations contain a chondromucinase which destroys metachromasia (120) may be unnecessary (126). Most tissue elements which stain with PAS,[2] including reticulin, become metachromatic if treated first with H_2SO_4; collagen continues to stain orthochromatically (112). Intravital staining of connective tissue with trypan blue depends on binding of the dye with glycoprotein in the ground substance (193).

The biochemistry of hyaluronidases is reviewed. They hydrolyze hyaluronate to a disaccharide by attacking only the N-acetylglucosaminidic bonds; β-glucuronidase contained in crude testicular extracts then liberates monosaccharides (135). The time required for reconstitution of the dermal barrier after depolymerization by hyaluronidase varies with age and, although prolonged during rheumatic fever and rheumatoid arthritis, returns to normal during convalescence or successful therapy (36). The acid mucopolysaccharide in the media of the human aorta increases in amount until the fourth decade and then diminishes (34). The synthesis of mucopolysaccharides decreases with advancing age (117). In the polymerized state, the ground substance of the symphysis pubis acts selectively as an ion-exchange resin for potassium; after depolymerization and uptake of water, this selectivity is lost (102). X-irradiation modifies the ground substance as shown by reduction in size of bullae formed by the subcutaneous injection of isotonic sucrose (60).

Fibers.—A profuse network of protofibrils with a diameter measuring in the millimicrons, is revealed in the ground substance by electron microscopy (203). After oxidation and impregnation with silver, Pahlke (150) differentiates precollagenous from collagenous fibrils. His precollagenous fibrils are similar in width to the protofibrils of other workers. Each protofibril may be a single polypeptide chain; to form reticular fibrils several are arranged in parallel so that their periodic patterns (about 640 Å) tend to match (26, 210). Theoretical configurations for the polypeptide chains are described (3, 154, 167).

Reticular fibrils with a width of from 100 to 500 Å are imbedded in an amorphous matrix of ground substance forming a membrane (119). This matrix is responsible for the argyrophilia of reticular fibers, is removed readily by water and salt solutions, and may include hyaluronic acid (98). The reticular fibrils are wound together into fibers. Some of the first reticular fibrils formed in the umbilical cord are built up from equivalent corpuscular units with a periodicity of 170 Å to 250 Å. The adult periodicity of 640 Å appears just before birth. During embryonic life, these fibrils increase in width and differentiate twice as fast in the umbilical cord as in tendon (167). The presence in the embryo and other rapidly proliferating connective tissues of fibrils with tapered ends (19) suggests that they grow by pyramidal accretion. Their incidence is not altered by the collagenous diseases (105).

Reticular and collagenous fibrils are structurally identical (14). Thus, collagenous fibers probably consist of reticular fibers packed closely together in a modified matrix. Reticulin and collagen contain galactose, glucose, mannose, and fucose (78). The greater concentration of these carbohydrates in reticulin may account for its more intense staining with PAS but it is not known whether the difference in their concentration is accounted for by the chemical composition of the fibrils or of the associated matrix. The carbohydrate fraction of collagen also yields hexosamine, tyrosine, and tryptophan (83). A globulin in antisera prepared against rat kidney reacts with reticulin and basement membranes, the antigen in which may be a mucopolysaccharide. This globulin does not react with collagen (49). Purified collagen is antigenic and exhibits species specificity (204).

Acidic citrate buffer extracts of connective tissue contain a precipitable protein which was designated as "procollagen" since more could be extracted from young than from old animals (148). The amino acid content and the uptake of radioactivity by various collagen fractions after feeding glycine-C^{14}, is compatible with the hypothesis that procollagen, most likely a fraction soluble at alkaline pH, is a true biological precursor of collagen (88). Conversion of procollagen would involve the addition of a fraction rich in tyrosine and poor in hydroxyproline, alanine, and serine (31). However, the physical similarity between collagen and the precipitates obtained from citrate buffer extracts of skin indicate that procollagen is not significantly different from collagen (26, 168) and, hence, may not be a true precursor.

All components necessary for precipitation of cross-striated fibrils from a solution of collagen are believed to be present in the extracted material (83). Precipitation is accomplished by changing the salt concentration or pH of the solution or by adding one of a variety of substances. With sodium thymonucleate, fibrin, and serum albumen, collagen fibrils of normal periodicity (640 Å) are obtained (167). The presence of polysaccharide either in the material extracted from skin or in the substance added, appears to be essential to formation, during subsequent dialysis, of long-spacing fibrils (about 2,100 Å) (67, 83). At low ionic strengths (NaCl) several polysaccharides precipitate fibers with no striations (83). In tissue culture, fibers are formed chiefly at sites giving an acid reaction (63).

Prior treatment of tendon with hyaluronidase increases the swelling of collagenous fibers, the solubility of collagen in dilute acetic acid and reduces the shrinkage temperature. Similarly, it facilitates the re-solution of collagen which has been precipitated previously from solution by addition of chondroitin sulphuric acid (99). Since hyaluronidase attacks chondroitin sulphuric acid, this polysaccharide probably is involved in intermolecular linkage of collagen molecules and lends stability to the fibers. Shrinkage temperature curves indicate that one-quarter of the stabilizing linkages are between chondroitin sulphate and collagen, 40 per cent being salt-like links and 60 per cent hydrogen bonds (100). In view of Meyer's hypothesis that aging of collagenous fibers involves a replacement of hyaluronic acid with chondroitin sulphuric acid as the substance which binds fibrils together (133), it is pertinent that the extractibility of collagen with dilute acetic acid (18) and the rate at which collagenase hydrolyzes human skin collagen (106) decrease with advancing age.

Analysis of the radioactivity of dinitrophenylglycine isolated from protein hydrolysates after feeding of glycine-C^{14} shows that the activity of collagen from skin, tendon, and bone is higher in young than in mature rats. Collagen is replaced slowly in the adult, but the turnover rate is low as compared with that of intracellular proteins (145). The incorporation of glycine-C^{14} is reduced by lowering the food intake but is unaffected by vitamin C deficiency (173).

The x-ray diffraction pattern of rat-tail tendon shows a meridian spacing of 2.86 Å which is not found with alpha- or beta-proteins. The infrared spectrum of collagen is characterized by the perpendicular dichroism of the N—H and C=O stretching frequencies and an abnormal value for the N—H stretching frequency of 3,330 $cm.^{-1}$ as compared with 3,300 $cm.^{-1}$ in alpha- and beta-proteins (3).

The elasticity of elastic fibers is abolished by dehydration or fixation in phosphomolybdic acid (159). Elastin may be a glucoprotein (156) or a lipoprotein (116). Physical measurements indicate that a soluble protein obtained from elastin undergoes reversible dissociation (30). In fish the pancreatic enzyme, elastase, is associated with the islets of Langerhans rather than with the acini (115). It is similar in action to bacterial chondrosulphatase and removes free acid mucopolysaccharides before attacking the elastic tissue itself (156). Prolonged digestion dissolves both the amorphous matrix of the fibers and its finest fibrils, indicating that either elastase is a complex of enzymes or that matrix and fibrils are of similar chemical composition (116). Elastic fibers may be composed of linear aggregates of a corpuscular protein unit protected on the outside by a layer of similar units bound together by union with a polysaccharide (85). In the absence of cement substance, it is no longer possible to differentiate collagenous from elastic fibrils by means of several histological methods (13). Elastic fibrils from the rat measure 350 Å in width and consist of protofibrils which are 80 Å in diameter; no cross-striations are present (12). The validity of the report that elastic

fibers possess a periodic cross-striation which is identical to that of collagenous fibrils (182) depends on a poorly understood differentiation of the two types of fibrils by silver impregnation.

Inflammation and Wound Healing

Proteases may be important in the induction of inflammation by bringing about the release of histamine, the physiology of which is reviewed (153). A parallelism exists between the capacity of numerous drugs to inhibit the protease, fibrinolysin, and inflammation (202). An increase in capillary permeability and attraction of leucocytes to an inflamed area are elicited by many polypeptides of large molecular size (142). However, these properties might be referable to their irritative capacity which induces the release of leukotaxine. Leukotaxine is found only in injured tissues, is of unknown chemical composition and is obtainable in crystalline form (130). An inflammation-producing material arises at the site of injury which migrates electrophoretically as a globulin (132). Regardless of the probable origin of chemotactic substances from injured cells, a factor is present in blood plasma which modifies the migration of leucocytes (109). During passive Arthus arthritis, a substance associated with mucoprotein appears in the blood and gives a color reaction with diphenylamine. It is an indicator of the intensity of the inflammatory reaction and is depressed by anti-inflammatory agents (45).

A nonspecific local resistance to inflammation is induced by injection of irritants into connective tissue. This protective response against a second inflammatory stimulus reaches its maximum 38 hr. after induction of the first inflammation and disappears in about five days (95). Granulomatous tissue forms a barrier against necrosis induced by chemical agents (184). Connective tissue cannot participate actively in phagocytosis and develop a protective fibrous wall at the same time (172).

Many factors modify the rate of wound healing. Exposure to stress (43) or the presence of skin wounds in rats during their late phase of closure (10) delays the healing of other skin wounds in the same animal. Nevertheless, the production of a substance by wounds which stimulates or inhibits proliferation of connective tissue is not established. The adequacy in the diet of S-containing amino acids is more important for promotion of healing than the total protein content (157). Following injection of L-methionine-S^{35}, more S^{35} appears in the wound as cystine than methionine, the rate of healing appearing to be a function of the cystine content of the wound (206). Ascorbic acid is essential to the maintenance of scar tissue since its deficiency causes fibroblastic proliferation, modification of the matrix, and hemorrhage in wounds which had healed under normal conditions for six weeks (160). Problems involved in homotransplantation are reviewed (53). Vascularization of a homograft conditions its capacity to initiate resistance in the host (131).

Although intense alkaline phosphatase activity is present in granulation

tissue of skin wounds at the time of fiber formation, one cannot conclude that it plays an essential role in fibrogenesis. Under special conditions, phosphatase is not histochemically demonstrable when fibers are formed (174). Experimental modification of the level of blood phosphatase or direct application of phosphatase inhibitors to wounds, fails to influence the rate of wound healing (81). Fibers which are precipitated from solutions of collagen in acetic acid bind alkaline phosphatase firmly *in vitro* (79a). This suggests that the enzyme associated with developing collagenous fibers (50) may be formed at some other site. Its absence in wounds of scorbutic animals (35) and in those treated with adrenal hormones (16a) may be secondary to the failure of the absorbing agent, collagen fibers, to form. The appearance of alkaline phosphatase in healing wounds can be correlated with the presence in the area of regenerating epithelium (68).

Some necrotizing or fibrosing lesions are characterized in their early stages by an excessive accumulation of acid mucopolysaccharides (128). The ground substance which stains metachromatically during the first four days of healing in skin wounds is hydrolyzable with hyaluronidase but, subsequently, becomes resistant (38). That demonstrated by staining wounds of scorbutic guinea pigs with PAS persists longer than normally and is neither metachromatic nor digestible whth hyaluronidase (32). At the time of fiber formation, ground substance increases in hepatic cirrhosis in relation to the cellularity of the connective tissue and decreases as the lesion becomes fibrotic (17). During the initial phase of healing after tenotomy, strands of fibrin are "spun out" by the action of muscle pull and serve to orient the fibroblasts which grow in from the surrounding connective tissues to effect repair. The metachromatic ground substance which then appears, persists for as long as a year (33).

The fibrinoid of rheumatic fever contains collagen, elastin, a polysaccharide, and a material rich in tryosine (47). It has the same isoelectric point as collagen and fibrin. Thus, its origin from one of the latter substances cannot be ascertained on this basis (189). The fibrinoid areas of a rheumatoid nodule give a distinctive x-ray diagram with a diffuse ring of spacing about 4.8 Å and provide no evidence for the presence of true fibrin (108). Histochemical studies indicate that fibrinoid consists of collagen fibers impregnated with a polysaccharide-containing material (79). As compared with aortae from young, healthy individuals, albuminoid (collagen, reticulin, and elastin) from aged and atherosclerotic aortae combines with larger quantities of HCl, contains more Ca and Mg, has a wider isoelectric range, and swells maximally at pH 12 (137). The birefringence of amyloid is attributable to the presence of masked fibers (138).

The Action of Hormones

Research on the homonal regulation of connective tissue has been concerned chiefly with adrenocortical steroids. Experimental clarification of the

action of hormones on connective tissue requires careful consideration of the dosage levels employed. Replacement of a deficiency with a "physiologic" dose usually elicits an effect which is different from that produced by the administration of larger amounts. Most recent studies deal with overdosage phenomena.

Cells.—Systemic or local administration of large doses of cortisone or hydrocortisone suppresses neoformation of fibroblasts in the repair of injured tissue. Because of the catabolic action of these hormones, it was suspected that they might act directly on the fibroblast. Attempts to clarify this point by use of the tissue culture technique have rendered exceedingly contradictory results because varied techniques and tissues have been employed and too little attention has been given to solubility of the hormones. In contrast to their acetates, the more soluble free alcohols of cortisone or hydrocortisone are more certain to suppress fibroblastic growth (104, 151), the effect not being strictly proportional to their concentration in the culture medium (37). At low concentration, cortisone fails to affect the total synthesis of RNA and DNA[2] but, when combined with growth hormone, increases the numbers of cell and the formation of lipid and RNA. Insulin stimulates growth (118). Desoxycorticosterone or DCA[2] may inhibit (23, 127) or stimulate proliferation of fibroblasts (124).

Experimental hyperadrenocorticalism *in vivo* reduces the tensile strength of healing wounds (2) and the collagen formation (125, 191) which is usually elicited by foreign bodies. Addition of cortisone acetate to a culture of fibroblasts depresses collagen formation if the tissue was obtained from embryos previously treated with cortisone (75). Retardation in wound healing is facilitated by protein depletion (65). Although modified by the total metabolic picture (199) the effect is not entirely secondary since the hormones are effective locally (41, 97). Adaptation with loss of inhibition eventually ensues (25). The degree of interference with wound healing varies with the state of nutrition, hormonal dosage, and species; it is rarely a significant problem during therapy of man with adrenocortical hormones. Because of the inadequate protection afforded by poorly developed granulation tissue, cortisone (190) and hydrocortisone intensify the necrosis induced by irritants, the inhibition in growth of connective tissue being counteracted by administration of somatotropin (186, 196). Treatment with cortisone prolongs slightly the period of survival of cutaneous homografts in some species (39) but fails in others, including man (205).

Granuloma formation is suppressed during pregnancy and lactation (136). Estrogens promote the healing of vaginal wounds (187). The collagen content of the uterus is increased during pregnancy (87) and in the skin of thyroidectomized rats by somatotropin (183).

The capacity of cortisone to suppress the migration of macrophages (16, 73) and neutrophiles (16, 76, 175) to a site of inflammation is established. Exposure of rats to stress and, under certain conditions, treatment with

adrenocortical hormones are reported to accelerate phagocytic acitivity (200). These observations are criticized (86) because large doses of commercial India ink were used (p. 63) and are not supported by the failure of cortisone therapy to facilitate the clearing of carbon (27), colloidal gold (74), and bacteria (44, 76, 175) from the blood. Cortisone does not affect the ingestion of staphylococci by peritoneal macrophages (74) but is reported to depress the clearing of polyphosphate macromolecules from the blood of dogs (70). Cortisone interferes with the intra-cellular digestion of bacteria (44, 122) and the regeneration of the reticuloendothelial system after blockade (27). Inpairment in the mobilization of phagocytic cells, the intracellular digestion of bacteria, and the formation of granulation tissue are among the factors which account for the increased susceptibility to certain infections which results from overdosage with adrenocortical hormones (198).

Failure to count the mast cells weakens the argument of Asboe-Hansen (6) that they are reduced in several species by therapy with corticotropin or cortisone, although others have demonstrated a reduction by this means (71). Cortisone reduces the uptake of S^{35} by mast cells (7). On the contrary, cortisone in tissue culture elicits only mild changes (151). Exacting counts reveal no significant change in the number of mast cells in several regions of rats (15, 54, 55, 181) treated with cortisone or hydrocortisone. Prolonged local treatment of the skin of rats with adrenocortical extract reduces the number of mast cells in the treated area only when other cellular constituents of the dermis are injured (15). Hence, it is doubtful if adrenocortical hormones exert a primary or significant effect on mast cells, although their responsivity may vary in different parts of the body or in different species. Administration of thyrotropin to guinea pigs appears to increase the number of orbital mast cells (8) but thyroxine has no effect on those in the skin of rats (54).

Ground substance.—The production of ground substance is stimulated by DCA *in vitro* (124) and in healing cutaneous wounds of the guinea pig (161). Its constituent mucopolysaccharides are increased in the retrobulbar connective tissue of the guinea pig by thyrotropin (8) and in the chick's comb by testosterone propionate (179). In contrast, cortisone suppresses elaboration of ground substance in tissue culture (124) and, at high dosage, *in vivo*. Concurrent local (162) or systemic treatment (179) with cortisone fails to counteract the stimulation of the chick's comb induced by testosterone. Thus, the capacity of adrenocortical hormones to inhibit fibroblastic activity is too limited to overcome the sensitivity of reproductive organs to stimulation by the sex steroids. Ground substance in connective tissue removed from animals treated with hydrocortisone or subjected to stress is coarsely granular when viewed with the electron microscope while that from normal animals is homogeneous or finely granular (4). The enhancement by therapy with cortisone (165) or x-ray (201) of growth and spread of transplanted neoplasms may be secondary to alteration in the connective tissue of the host.

These evidences of change in the ground substance suggest that adrenocortical hormones modify the permeability of connective tissue. Adrenalectomy accelerates the rate at which intradermally injected indicators spread (158) while overdosage with cortisone increases the resistance of skin to the injection of fluids (207). Local treatment with adrenocortical extract does not alter the spread of intradermally injected hemoglobin (91).

The spreading action of hyaluronidase is not accelerated by adrenalectomy of the rat (155). The effect of hyperadrenocorticalism depends chiefly on the duration of hormonal action on connective tissue prior to the test (48) and on the concentration of adrenal steroids at the time of the test. Acceleration in the rate of spreading is observed in rat skin after prolonged local treatment with hydrocortisone, cortisone, DOC[2] (90), or systemic injection of large doses of adrenocortical extract (91) or DCA (28). Therapy with corticotropin or subjection to stress for prolonged periods is ineffective (28).

In contrast, inhibition in hyaluronidase spreading action occurs if the level of circulating steroids is raised abruptly with insufficient time being allowed for modification of the structure of connective tissue (91) before the test is carried out. Prior treatment with corticotropin for only 24 hr. inhibits the spreading action of hyaluronidase in living rats but not if the rats were killed just before the test (40). In rabbits, a short period of administration of corticotropin or exposure to cold, inhibits the spread induced by hyaluronidase or streptococci (28), the magnitude of the effect being inversely related to the duration of the hormonal treatment. *In vitro* under physiological conditions of ionic strength and pH, both cortisone and DCA inhibit hyaluronidase; at about pH 6, DCA has an accelerating effect which is antagonized by cortisone (56).

The local application of estradiol to the skin of rats accelerates the rate of spread induced by intradermally injected hyaluronidase. In contrast to the adrenocortical steroids, this effect is not limited to the area of application but occurs in other areas of the body also (90). The spread of hemoglobin with or without hyaluronidase, is suppressed during late pregnancy, and the rate of absorption of intradermally injected fluorescein is accelerated (163). Nonspecific hyaluronidase inhibitor, the level of which in the serum is under pituitary-adrenal control (80), increases during human pregnancy (163). Since the inhibitor is probably a heparin-lipoprotein complex, mast cells may be its origin (181). The mammary gland contains an extractable spreading factor, the elaboration of which appears to be under hormonal control (62).

Inflammation.—The anti-inflammatory properties of adrenocortical steroids are attributable to their capacity to suppress the responsivity of connective tissue to substances released by injured tissue (149). In general, their effectiveness is inversely related to the strength of the inflammatory stimulus. Blood vessels constitute an important focus of action. In human hypopituitarism, corticotropin and cortisone increase, and DCA decreases the resistance of capillaries to negative pressure (176). The period of ex-

tremely low capillary resistance, which follows exposure of rats to stress, is prevented by treatment with cortisone. In adrenalectomized rats, cortisone raises the capillary resistance but fails to do so if somatotropin is given concurrently (111). Cortisone-like steroids counteract the increase in capillary permeability induced by leukotaxine (129), peptides (20), and histamine (42). Cortisone induces an excessive tonicity of the capillaries which feed advancing endothelial sprouts in growing granulation tissue. These vessels contain little blood. The reduction in capillary permeability and in flow of blood may prevent adequate nutrition of the adjacent connective tissue (9). The anti-inflammatory action of hydrocortisone is enhanced by the reduction of blood flow to the inflamed area (185). Nevertheless, some of the anti-inflammatory function of the hypophysis is probably carried out independently of the adrenal glands (92). Hypophysectomy decreases the volume of the exudate (1) and general intensity of the inflammatory reaction (94).

Somatotropin alone elicits arthritis in rats (169). The validity of the Selye hypothesis that human collagen diseases are the result of disordered adaptation to stress is questioned (24). Combined treatment with sodium caseinate and cortisone or nitrogen mustard induces amyloidosis (197).

In conclusion, recent research emphasizes the significance of mucopolysaccharides as structural components of connective tissue fibers, but the precise role played by the fibroblast in fibrogenesis remains unknown. The mode of formation of ground substance is still debatable. The vascular effects exerted by adrenocortical steroids are of great importance in explaining their anti-inflammatory power but the nature of their direct action on the fibroblast is not clear.

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HEAT AND COLD[1]

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Restless man roams the desert, the Arctic waste-land, the sea, and the sky, his naked protoplasm protected against immediate disaster by a thin layer of keratinized epithelium, a minute microclimate, and a varying "pelage" of his own ingenious creation. He has learned much about the extent of his heat exchanges with the environment and their physical partition, but he knows very little concerning the transients involved. The dimensions of his microclimate, so important to his survival as well as comfort, and the topographical variations in its dimensions over his body pose observational problems whose solutions require the highest level of inventiveness in experimental design. The static observational approach has largely ignored the sequence of events through which his thermal state alters or remains relatively constant. Transients are of the essence of homeostasis; their instantaneous magnitude and direction become determinants of vascular convection of heat, sweating, shivering, and possibly visceral production of heat. Observational requirements currently dictate fragmentation in the study of these items, but correlative integration is the actual dynamic characteristic of the thermal homeostatic mechanisms. Hence, distinctions between "basic" and "applied" research in this field become irrelevant. The technical requirements of the military services actually offer opportunity for the execution of difficult experiments having great theoretical interest and significance. Thus, why is peripheral vasomotor tone apparently lower in the cold-adapted Eskimo than in the nonadapted urban dweller when exposed to comparable cold? Why do some persons sweat sooner and more readily than do others when exposed to comparable heat? Why are the temperatures of the American home, so comfortable from the American point of view, also so disagreeably hot to the English? Naming the differences as "adaptation," "acclimatization," "conditioning," neither identifies nor analyzes the basic phenommena involved.

Heat Exchanges

Methods.—Methods of measuring climatic variables, respiratory exchange, energy metabolism, skin temperature, and sweating are described briefly in the new volume in the series *Methods in Medical Research* (1). An ingenious electric hygrometer of the Dunmore type has been fitted inside the end of a hypodermic needle (2) offering the possibility of an elegant method for studying the microclimate of the body. Radiometric methods have been adapted to the measurement of the radiant temperature of the

[1] This review covers the period August, 1951 to July, 1954. No reference is made to abstracts of papers presented at Society meetings or Congresses.

environment (3) and of the skin (4) and to the rapid recording of skin temperature (5). Thermistor thermometers (6, 7), a rectal thermocouple catheter (8), needle thermocouples (9), continuous recording devices (10), heat flow discs (11, 12), a recording digital calorimeter (13) extend the instrumentation. Short range variations in skin temperature have been computed from incoming radiation and coefficient of absorption after allowing for heat loss by radiation and evaporation (14); these data should be compared with the direct measurements of skin temperature with rapid methods (5). Photographic technics permit the determination of body measurements, surface area, body volume, and its radiation area (15, 16, 17). The latter varies between 65 and 77 per cent of the total area, depending on posture (couched to erect), and is unrelated to body type (17). Three new methods for calculating the surface area of the body are described by Schmitz (18). The principle of the temperature gradient calorimeter has been applied to regional heat loss measurements in man (19). Cooling gradient calorimetry may be adapted to the study of local vascular changes (20).

Deep body temperature.—Measurements, in the field, of the deep body temperature of arctic and subarctic mammals and birds demonstrated its remarkable constancy even in intense cold, the prevention of rapid cooling by the thermal mass of the body, particularly in large animals, and that the temperature of a species in the field is characteristic of that species (21). This observation bears on the apparently random relation between body temperature and body weight (22). Further data are available on normal temperature ranges in man (23, 24), on deep tissue temperature (25 to 29), rat's average body temperature when cooled (30), effects of anesthesia (31), and diurnal rhythms in body temperatures (32, 33).

Heat transfer.—Various calorimetric experiments in the past have utilized the basic heat flow equation for calculating either heat storage or changes in body temperature. The theory of heat exchange in a hot environment has been developed at length in an extremely useful report by Woodcock *et al.* (34). Various forms of this equation usually include the effects of air temperature and velocity. However, during moderate work at various saturated air temperatures and velocities (35), body temperatures stabilized within 1 hr. at levels which were independent of air temperature and velocity in the range of from 83° to 90°F. and from 50 to 400 ft. per/min. Increased work rates lowered the saturated air temperatures to which this statement applied. Above saturated 90°F., body temperatures took longer to reach equilibrium values and also were higher, depending on wind velocity. Maximal sensitivity of sweating and heat transfer to the skin when rectal temperature was in the range from 99.4° to 99.9° F.would minimize environmental effects on heat transfer. Increases in body temperature beyond this zone resulted in less effective physiological adjustments, and air velocity and temperature became increasingly important in heat transfer (35). Precise separate determinations of radiation and convection in the clothed subject by Nielsen & Pedersen (36) indicated that air velocities up to 24 ft. per/min.

had little effect on convective transfer which at these low velocities depended principally on the air movement resulting from the temperature difference between the body and the air. The composition of the microclimate, convection, and evaporation, therefore, depend on this aerial temperature gradient. This point bears on efforts in this laboratory (37) to estimate regional rates of heat transfer by the method of partitional calorimetry. Further studies of the effects of clothing on sensible heat loss and evaporation are available in declassified reports (38, 39). Women eliminate less heat in the cold zone because of lower skin temperature and conductance; they produce less heat in the warm zone and show higher skin temperature and conductance and less sweating (40). Whether these differences between the sexes are sexual or the result of "conditioning" of the body "thermostat" deserves study. The usually large deposit of cutaneous fat in the female may be responsible since the insulative effect of fat increases as ambient temperature falls below 70°F. (41). The lowering of shivering thresholds by fat (41) complicates interpretation. The measurement of body fat by the skin fold technique is apparently successful in the absence of heat stress but in error when marked cutaneous vasodilation occurs (42). The thickness of fat on the back correlates quite well with the fat content of the body (43). The parameters of time, thermal conductivity, specific heat of the skin, reflectance, and absorption have been evaluated in an able study of penetrating flash radiation effects by Buettner (44). The calculated temperature data permitted satisfactory predictions of the depth and degree of tissue necrosis.

Air conditioning function of the upper respiratory mucosa.—This has been confirmed by Cole (45, 46, 47) through the use of a fast sensitive thermistor device which showed that most of the conditioning of the inspiratory air occurred before it reached the trachea; increased ventilation, cold, or both, shifted this zone downwards into the trachea. This type of observation is astounding when one calculates the linear velocity of air flow in ordinary breathing over the mucosa. Although the ratio of nasal surface to skin surface is relatively small in man (48), heat losses from the upper respiratory passages can rise to high values in the cold and become important in determining caloric requirements and survival time in the cold (49). Nevertheless the cooling effect of exposure to cold on the pulmonary blood is quite small (50), only 0.03°C. The term "pulmonary heat loss" is anatomically inaccurate as it is usually used. The speed of humidification of inspired air is confirmed by studies on the respiratory absorption of HTO (water-t) (51).

Insensible perspiration.—The processes of insensible perspiration have received considerable attention. Rothman (52) in his new book on the skin includes physical (diffusive) water transfer and low rate sweat secretion in this term. Areas of "low electrical skin resistance" on subjects at rest in ambient temperatures below the so-called sweating threshold favor Rothman's point of view. Possibly the very competent study of Thauer & Zöllner (53) on the relation of insensible weight loss to the vapor pressure of the air at different temperatures involved the deceptive presence of varying but

undetected sweating, particularly on the palm and sole. Reference to the regional rates of evaporation as measured with the desiccating capsule technique in this laboratory (54) indicates that the rate of insensible water loss from the palm and sole may be a hundred times as great as that from other areas of the body and amount to one-half of the total cutaneous insensible water loss. It is a simple matter to demonstrate the dependence of the plantar and palmar rates on ambient temperature. Buettner (55) has studied the "diffusion" of water and water vapor through human skin, formulated equations which are possibly descriptive of the process, and concluded that a two-way process of water transfer may occur and account for the surprising inhibitory effect of humidity on sweating (measurements made at the same skin temperature). He further suggests that data on sweating and water transfer as obtained with desiccating capsules may be in error because of the effects of the capsular microclimate on the repenetration process. A recent study by Randall *et al.* (56) of the performance of such capsules does not seem to answer this criticism adequately. Recognition of the repenetration process is complicated by the hydrophilic properties of the stratum corneum, the water content of which is influenced by temperature and humidity (57, 58). Schmidt-Nielsen & Taylor (59), using an elegant quartz fiber microbalance, found a steep rise in the water content of this layer, with the maximum at about 0.2 mm. from the surface, as one might expect from evaporative data. Keratinization of the cells of the sweat duct during its passage through the corneum (60) offers the possibility that invisible sweating may moisten the corneum to varying degree. Folk & Peary (61) appear to have demonstrated water repenetration into the foot as an important factor in the operation and design of foot gear. Various service laboratory reports describe field experience with vapor barrier boots in which long continued excessive hydration of the corneum is a troublesome feature (62).

Heat

Thermal tolerance.—Thermal tolerance depends on many factors. Craig *et al.* (63) studied the performances of clothed, trained, and acclimatized men working in a warm (29° to 37°C.) room. Voluntary tolerance time correlated best with the heat load expressed as heat storage in kcal. per sq. m., was characteristic of the subject, and independent of the rate of storage, and also correlated well with the calculated time to reach a heart rate of 160. The body temperatures reached in acclimatized (64) and unacclimatized (65) African laborers when performing standard work at various saturated air temperatures and velocities were determined by the work rate in mild conditions (86°F. saturated or less) and not by the ambient temperature. At levels of the latter above 86°F., internal and external heat loads progressively increased body temperatures until an equilibrium was no longer possible. The unacclimatized African exhibited higher body temperatures and heart rates at the same working rates and air temperature, attributable probably to a smaller sweating response which in the acclimatized African was fully three times as great as in the heat-acclimatized Englishman (65). One may

note that the increments in sweating per increment in body temperature were about the same in both groups of Africans. Does this imply a lower sweating threshold in the acclimatized African? The net result of acclimatization made it possible for the latter to work safely at saturated air temperatures 3° to 6°F. higher than could the unacclimatized subject. Sick men with rectal temperatures of 100°F. or higher showed a decreased tolerance for the combined stress of heat and work (66), rectal temperatures rising to higher and distressing levels, but it is not clear from the data presented whether the temperature rise in the sick and well subjects proceeded in parallel fashion, the sick possibly differing only in the starting temperature. The difference in discomfort obtaining with increments in rectal temperature resulting from work or external heat load is well known. The Finnish Sauna bath (67) to which I had been accustomed in my youth seemed relatively agreeable even though high sweating rates were probably reached. I have also noted that the discomfort of resting subjects exposed repeatedly to a hot climate chamber tends to diminish as their attitude towards the experiment becomes more passive with experience, although skin and oral temperatures and sweat rates are the same in comparable experiments. The experiments of Lee (68) are especially interesting because of the exceptionally high body temperatures (41°C.) induced in his patients by external heat load and its long duration (6 to 7 hr.); mental depression appeared in the subject after about an hour, followed by a kind of recovery. There was no evidence of heat stroke; sweating (forehead) continued at a high rate.

Patients with congestive heart failure tolerate hot humid surroundings much less readily than do normal subjects and often exhibit acute attacks of left ventricular failure, apprehension, and panic (69). There also seems to be an increased frequency of acute myocardial infarctions during summer months in a warm climate (70). Certainly, clinical experience in St. Louis verifies the general impression that these patients have less tolerance for heat and that the hospital admissions of these patients rise during periods of hot weather. Although such items as a possible increase in cardiac load from cutaneous dilation and increase in circulating blood volume have been conjectured in explanation, there does not appear to be a systematic analysis of this situation. Heat stresses by eliciting sweating and increasing cutaneous blood flow tend to produce reciprocal effects in the kidney (decreased urine and renal blood flow), particularly when superimposed on heavy exercise (71). Antidiuretic substance appears in the urine (72, 73). It would be interesting to know if these effects, observed in the normal subject, are augmented in cardiac patients. Kanter (74) has shown that heat depresses chloride excretion in the dog's urine, independently of the degree of hydration. This effect disappears when the dog is removed to a cool environment; its drinking in the heat is often inadequate to replace water losses; the drinking patterns vary.

Sweating.—This topic continues to excite wide-spread interest. Randall has published a convenient review of its physiology (75).

Several lines of evidence from this laboratory indicate that sweating is

recruited first over the most distal areas (dorsum of foot and hand) thence ascending the body surface to higher levels. This seemed to be the case whether equilibrium values (54) were used to support the statement or recruitment was followed during increasing ambient temperature (76, 77). Sudden exposure to high temperatures obscured the process completely, all skin areas recruiting at once (77). This phenomenon of the sequential recruitment of individual glands seems to vary markedly among individuals; some subjects exhibit it much more than do others. Although our inclination has been very strong to consider the topography of sweating responses as being expressive of processes of central facilitation resulting in the activation of some sudomotor fibers and not others, Dole & Thaysen (78) using a very delicate modification of the iodine-starch-paper method did not observe variations in the number of active glands during either thermal or mecholyl induced sweating although outputs varied; the thermal stress (105°F.) was too high, however, to permit observation of topographic recruitment; neither did they extend observations simultaneously to many areas.

The studies of Herrmann, Prose & Sulzberger (79) on the topography of thermoregulatory sweating are difficult to interpret because of the absence of data on body temperatures and heat load (which was applied by light bulbs). Nevertheless they noted regional differences in the onset and level of sweating, variations among individuals, asymmetry in sweating, and differences between the sexes. Axillary sweating in heat and emotions has its origin in different glands, the adrenergic apocrine glands not responding to heat which elicits profuse sweating from the numerous cholinergic eccrine glands (80, 81). Mean body sweat rates considerably exceeded arm rates (measured with the arm-bag technic) in unacclimatized subjects, but the difference diminished with rising thermal stress (82). Acclimatization also decreased the difference in rates, suggesting regional redistribution of the sweating response. Palmar sweating is again reported as not being increased by heat (83), but palmar, plantar, and axillary bursts of sweating are said to occur during or just before shivering (84). Benjamin's studies (85) of the sweating responses to quantitated local heat applications to limited areas (5×5 mm.), and their modification by locally applied drugs and environmental temperature and humidity, suggested that the effects of arriving sudomotor impulses could be facilitated locally at the gland level. It is not known how important this might be in accounting for the topography of thermoregulatory sweating. The actual temperature threshold of the gland seems to be too high (38°C.) to be significant in the usual recruitment of sweating.

A method of collecting sweat in pre-weighed discs of filter paper permits simultaneous measurements of the volume and composition of the sweat secreted over small areas (86); Dole *et al.* (86) believe that the decreased response of the glands to repeated injections of cholinergic drugs is evidence of "fatigue."

Studies of the distribution and number of functioning eccrine sweat

glands may be effected by means of plastic impressions of the skin (87) and also by the deposition of metallic silver or filter paper (88). Another novel method (89) utilizes a combination of photo- and aqueous sensitivity (complex double iodide of silver and mercury) to secure prints of active pores on paper. The cobalt chloride test has been developed further (90).

Comparison by Thomson (91) of the number and distribution of functioning eccrine glands with regional sweating rates indicates that topographical differences in sweating arise in the manner in which sudomotor neurones are recruited rather than principally in local glandular differences. This seems to apply also to differences in the total sweating rates of Europeans and Africans (91); there does not appear to be any significant difference between the two races with respect to the number and topographical distribution of sweat glands. The cold-adapted Japanese Aino were unable to recruit as many sweat glands (counts made by Jorgenson's method over entire body) as did other Japanese when "maximal" sweating occurred (92). This might mean either a smaller number of glands per unit of skin surface or that cold adaptation interferes with sudomotor recruitment. Racial and individual differences in sweating may be both functional and anatomical in origin. The number of sweat glands, the number recruited, their mean size and output, the maximal available recruitment—these items require information which is not now available in adequate extent. A major difficulty in the study of the topography of sweating is the occurrence of the "pressure sweat reflex" (93, 94); unilateral pressure on the body such as that resulting from the subject lying on his side results in a contralateral increase in sweating and ipsilateral depression; the effect is immediate and reversible.

Cycling seems to be characteristic of the discharges of the sweat pores. Long and short cycles have been described (94). They usually occur synchronously on different areas, but asynchronous discharges also appear. The mean effect of cycling may be followed by the method of electrical skin resistance (95). The phenomenon may be attributable to variations in the sudomotor impulse traffic. However, the contractility of the myoepithelial cells, as has been demonstrated by Hurley & Shelley (96) in the instance of axillary apocrine glands, may result in periodic ejections of fluid to the mouth of the sweat duct. Such cycles would necessarily be brief. Duct contractions could not account for the longer cycles having a duration of twenty minutes and involving a doubling of sweat rates (94). Although these cycles must have at least a slight effect on body temperature, they should not be attributed to "hunting" by the body's "thermostat" except in the sense that sudomotor discharges may be elicited, when body temperature is high enough, by various sensory and psychic influences which impinging on the sudomotor pathways facilitate activity already under way.

One generally says that sweating increases in a humid atmosphere. This statement apparently may be either true or false depending on qualifying additions to it. Taylor & Buettner (97) compared sweating rates in dry and

humid climates at the same skin temperature, and found them to be lower in the more humid environment; this seems to hold in resting or exercising subjects; this effect would be importantly significant in temperature regulation, if really true. Various possibilities, such as repenetration of water, cutaneous storage of water, and diffusion, were considered in accounting for the "apparent" inhibitory effect of humidity on sweating. However, the relating of sudomotor drive to skin temperature is open to criticism. Opinion generally attributes this to central temperature, although cutaneous thermosensory recruitment and inhibition of sweating has been demonstrated in a number of ways in this laboratory (98). Another possibility in accounting for the inhibitory effect of humidity is suggested in the observation by Shelley (99) that keratotic plugging of the pore of the sweat duct inhibits the gland's secretory activity, as indicated by the glycogen levels of the secretory cells. Clinical experience with the sweat retention syndrome (100 to 104) affirms the importance of air temperature and humidity in its incidence and treatment; interpretation of the data has attributed the syndrome to peroral closure of the sweat duct by wet plugs. It is not known how rapidly peroral closure may be effected by moisture. The phenomenon is readily demonstrated on the palm and sole but less certainly on other skin areas (58).

The recent review on the composition of sweat by Robinson & Robinson (105) reduces the need for the consideration of this topic here. They make the point that the sodium chloride content of sweat is affected by neither heat nor acclimatization *per se;* body deficits in salt may result from heavy sweating and elicit salt retention which is related only indirectly to the heat load; adequate salt intakes prevent body retention and fall of chloride in sweat and urine concentrations; these results of sweating proceed from the effects of the resultant varying salt load on the pituitary-adrenal system. Bass *et al.* (106) disagree. They obtained no evidence of increased activity of the pituitary-adrenal system (eosinophiles, urinary 17-ketosteroids) in an elaborate and exhaustive study of body fluids and electrolytes during acclimatization to heat. The concentration of electrolytes in sweat fell progressively during the first week of heat. Their data would appear to be decisive except for errors inherent in the arm-bag method of collecting sweat for analysis (107). However, if one assumes that these errors operate uniformly, one must accept the directional implications of their sweat data. Additional information is available in studies on the effects of the Finnish "Sauna" bath (108, 109). Basic differences between the sweat gland and the renal tubule appear in the excretion of urea (110); the ratio of urea concentration in the sweat to that in plasma remains relatively constant despite a twenty-five fold variation in the latter; the concentration of sweat urea was independent of sweat rates. However, Araki & Ando (111) believed that they had evidence that the sweat duct may reabsorb water and in this sense behave analogously to the renal tubule.

Bass *et al.* (106) demonstrated that body fluids undergo systematic

changes during acclimatization to heat: the extracellular fluid compartment expanded isotonically as a result of renal retention of sodium and chloride in excess of that lost in the sweat; plasma volume expanded even more initially; circulating protein also increased initially; total body water and "intracellular water" changed little. Itoh (112), reporting on the results of a field study in Japan and Formosa in 1942, states that an excess of chloride remained in the body after heavy sweating for from 3 to 8 hr.; yet, there was no increase in blood chloride. He suggested an outflow of intracellular water and deposit of chloride in the skin in accounting for the observations; however, data on "intracellular" water and the fluid compartments (106) do not support his interpretation. Following heavy sweating (3 to 5 kg.), the largest fraction (60 per cent) of the water loss is supplied from the thiocyanate space and only a minor fraction (10 per cent) from the blood volume (113). Nevertheless, the decrease in the latter is equivalent to an ordinary blood donation; coupled with cutaneous venous dilation it could reduce cardiovascular acceptance of such other stresses as exercise and the feet-down position. Sjöstrand (114) in his review on blood volume has emphasized the importance of vasomotor tone to the hydrodynamic balance between blood and tissue fluids and therefore to the level of blood volume. Current data suggest that the initial expansion of the extracellular compartment (including plasma) is followed by increased hematopoiesis. The process could be initiated by decreased vasomotor tone in the skin.

Cutaneous blood flow.—Theoretical relations between cutaneous blood flow, surface and subcutaneous temperatures, and conductance have been reviewed by Hertzman (115). Simultaneous measurement of skin temperature and blood flow in toes (116) yields the same curvilinear relation as that predicted from theoretical considerations (115). Conductance on the trunk, arm, and leg rises almost linearly with the ambient temperature (above 24°C.) while on the palm and sole the relations are more complex (115). Rates of arterial perfusion of trunk, arm, and leg skin parallel closely the conductance data on these areas. The increment in cutaneous blood flow with surface temperature amounted to about 9 $mm.^3$ per $cm.^2$ per min. per °C. which would result in maximal dilation (according to earlier data from this laboratory) when $T_S = 45$°C. Calculations of local conductance from Benjamin's data (117) on the temperature gradients in the skin during local heating agree. Celander & Folkow (118) indicate that the increase in cutaneous blood flow on heating the skin is the result of a direct effect on the vascular smooth muscle. Dilation in the foot developed somewhat differently during local heating (119); flow rose sharply beginning at a temperature of 30°C. The changes in blood flows in the palm and sole differed markedly from those in trunk, arm, and leg skin during exposure to general heat (115). The palmar and plantar dilations appeared to be more abrupt and reached maximal values much earlier (30° to 34°C.). Palmar dilation preceded plantar (115). The same sequence was seen by Catchpole & Jepson (120) during body

heating. I submit that these observations negate important thermoregulatory adjustments of the cutaneous blood flow in the trunk, arm, and leg by vasomotor nerves, that the level of flow here is set largely by the local skin temperature, and that palmar and plantar rates of blood flow depend principally on the innervation of the vessels in the palm and sole. Ederstrom (121) observed somewhat analogous regional differences in blood flow in the dog during the hyperthermia resulting from radiant heat or dinitrophenol. The simultaneous onset of panting and marked vasodilation in the tongue is most striking. Extremity venous pressures have been followed in men exposed to a hot humid environment (122); they should be correlated with hand and foot blood flows. Measurements in this laboratory by Cooper *et al.* (123) of the surface temperature and of the volume pulses of the skin directly overlying active muscle indicate that venous convection may transfer relatively large amounts of heat directly to the skin without first returning to the heart. The required venous channels exist.

The peripheral vascular responses to heating limited areas of the body deserve mention. A heat cradle over the whole trunk increased the clearance of Na^{24} from hand skin; the results on muscle were variable (124). "Reflex heating" increased extremity flow but decreased renal flow in normal and and hypertensive patients (125); the inverse effects on renal and extremity blood flows have appeared in earlier studies on the effects of heat. Certain cases of obliterative arteriosclerosis exhibited delayed and decreased responses to reflex heating (125). Cooper & Kerslake (126) suggested that an important afferent component in "reflex heating" is interrupted by sympathectomy. Their published data are not striking. Case selection left much to be desired. Their experiment should be carried out on young men sympathectomized for reasons other than vascular disease. Blood flow to extremities may be increased significantly simply by conserving body heat by enclosing the lower extremities in insulated plastic boots (127). Experience with vapor-barrier footwear suggests caution in using this application.

There are many reports on the thermal, vascular, and biological effects of ultrasonic irradiation. The subject has been reviewed by Wakim (128) and Fischer (129). Increase in blood flow is proportional to the rise in tissue temperature (130). Further data are available on tissue temperatures following microwave irradiation (131). Muscle blood flow (132) increased when muscle temperature reached a critical temperature of 44°C. which seems very high for initial dilation.

The thermal behavior of arteriovenous anastomoses in the skin has been studied further. Using the relative passage of pellets and Evans Blue as an indication of the constriction or dilation of these vessels, Bostroem & Schoedel (133) inferred that they dilate with local warming, acetylcholine, and denervation, and that they constrict with local cooling and epinephrine. Stein & Schroder (134) recorded capillary and venous pressures in the forelimb and concluded that the reactions of these vessels in the temperature range of 10° to 35°C. were shared by the total vascular bed and that there-

fore no specific role in temperature regulation could be assigned to these vessels. It would be interesting to relate their behavior to the foot and hand edema of hot weather.

Cold

Various methods have been used in cooling the human subject or animals: immersion, hollow blankets containing a system for circulating cold liquids, and cold air. A unique method cools the venous blood stream on its return to the heart; this procedure produces a rapid drop of the internal temperature (135). Premedication with morphine, atropine, pentothal, ether, etc. establishes light anesthesia before chilling and prevents vagal cardiac reflexes. Surgical interest views hypothermia as an important adjunct in surgery of the cardiovascular and pulmonary systems and of the brain (136 to 143). Since fall in body temperature reduces metabolic rate and the requirement for the circulation of the blood, there is practical significance in the questions: what is the lethal level of hypothermia? what factors influence this level? Variations with species, the presence or absence of anesthesia, the level of respiration, use of intracardiac catheters, medication prior to chilling, substitutional perfusion of the coronary and cerebral vascular beds, all determine tolerance to hypothermia and subsequent recovery from it. Hegnauer *et al.* (144) report 16°C. as the lethal temperature of the anesthetized dog but others (145) have cooled anesthetized dogs down to 12°C. or even lower with complete recovery. Respiratory acidosis in anesthetized dogs is an important factor in lowering their resistance to immersion hypothermia (146, 147); premedication with sodium bicarbonate increased their tolerance (146). Maintaining pulmonary ventilation and the circulation is emphasized by most investigators of hypothermia, but Rosenhain & Penrod (148) consider the respiration as adequate until near the point of final collapse. Cardiac arrhythmias, particularly atrial fibrillation in man, and ectopic ventricular beats passing into ventricular fibrillation in the dog, are decisively limiting factors to survival during hypothermia. Juvenelle *et al.* (145) emphasized that fibrillation *per se* is not injurious, providing the coronary perfusion is adequate. The occurrence of fibrillation despite perfusion of the coronary system tends to eliminate cardiac hypoxia as the reason for its onset. Intraventricular catheters, inserted to record pressures, may induce idioventricular ectopic beats followed by ventricular fibrillation (149). This apparent sensitization is not related to hypoxia, since administration of 100 per cent oxygen did not affect the onset of the arrhythmias (149). Ventricular fibrillation also results from focal cooling with a small thermode having a contact area of only 1 $cm.^2$; astonishing effects on atrial rhythm also appeared (150). One may well ponder a situation in which myocardial irritability to thermal and mechanical stimuli seems enhanced while impulse generation progressively diminishes with resultant lengthening of diastole to cardiac standstill (144). At any rate, a defibrillator would appear to be essential accessory equipment when hypothermia is employed. The

technical problems of adequate aeration of blood and perfusion (151) should be more easily handled when lowering of metabolic rate by hypothermia decreases requirements. Thus, the mortality from complete ischemia of the liver for 1 hr. is reduced if body temperature is lowered to 26° to 28°C. (152). Not only does cold complicate the respiratory adjustments to hypoxia (thus witness the need for artificial respiration) but the latter complicates the thermoregulatory adjustments to cold (153).

The exposure of the unanesthetized animal to cold results in somewhat different data. Thus, the shaved dog, exposed to an ambient temperature of −30°C., ate, shivered almost continuously, and maintained its deep body temperature within 1.5°C. until less than 2 hr. prior to death (154). Incoordination and disorientation appeared just before the fall in body temperature which remained unexplained. Adolph's studies (155) on infant cats, hamsters, rats, mice, rabbits, and guinea pigs demonstrated that the lethal temperature rose with increasing age in all species and that the adult patterns of changes in heart rate and respiratory rate with cold exposure emerged at the end of serial modifications. The hamster was found to be somewhat more resistant to cold than the rat (156); its lethal colonic temperature was about 3.8°C. The ability of the unanesthetized rat to maintain its mean arterial blood pressure during fall in body temperature showed little impairment, despite progressive slowing of heart rate, until colonic temperature was reduced to near the lethal level (14.7° to 18°C.) when the arterial pressure dropped precipitously. There was no difference in the time-pressure curves of animals dying and surviving. Pentobarbital anesthesia increased the rate of the pressure drop (157). Although restraint decreased the cold tolerance of rats, this effect may be diminished through a process of daily "conditioning" (158). The lower limit of body temperature of white footed mice at cold death was about 4° to 5°C. (159). Hypertensive rats do not tolerate extremes of temperature (5°C. and 35°C.) as well as do normal rats (160). Revival of hypothermic rats has been effected even after the heart had stopped (161); the first heart beat appeared when colonic temperature had risen to 5°C., respiration returned at 13° to 15°C., and muscle tone, reflexes, and "consciousness" later. Radio-frequency rewarming was effective in reviving monkeys and dogs (162). X-ray irradiation increased the mortality of rats from cold (163), but the latter protected mice (164) and rats (163) against the former. On rewarming cold dogs by placement in a 45° bath, recovery in arterial blood pressure, pulse rate, P-R, Q-T, duration of systole, and isometric relaxation mirrored the changes occurring in the same items during cooling (144). The increments in heart rate with rise in temperature vary at different levels of body temperature (165).

Peripheral circulatory responses to cold.—In a survey of the literature on the effects of different ambient temperatures on manual and pedal blood flows, Hegnauer & Angelakos (166) state what appears to be a generally accepted conclusion: reduction in these flows conserves body heat; hence, a protective vasodilation in these parts requires that the entire body be warm;

changes in digital blood flow are attributable principally to vasomotor reflexes on which may be superimposed the direct effects of cold on the blood vessels, particularly the arteriovenous anastomoses. The possible far-flung character of the vasomotor reflexes elicited by cold stimuli applied to the skin is illustrated in the increases in rectal (167) and gastric (168) bloodflow. Although vasomotor tone tends to rise earlier in the toes than in the fingers of nude subjects during their cooling, Hall *et al.* (169) find that manual skin temperatures of clothed subjects immersed in cold water falls more rapidly when the insulation of the feet and hands is about the same; this difference may not reflect corresponding vasomotor and vascular changes but rather the operation of the thermal "sink" which is considerably larger in the foot and leg than in the hand and arm.

Using an index of resistance to cold based on changes in digital temperature, Yoshimura *et al.* (170, 171) observed that digital tolerance for cold was influenced by many factors (age, sex, race, training, "autonomic balance" and that it was especially increased by a high protein diet which seemed to be protective against frost-bite. Application of the principle of gradient calorimetry did not reveal any essential differences in the effective thermal conductivity of normal and rheumatic tissues in response to cooling (172); however, Reader (172) did obtain a higher value for the thermal conductivity of skin without blood flow than that previously reported and observed that its thermal conductivity rose considerably with increase in its water content. A hyperglycemia following a partial cold bath seemed to favor recovery in skin temperature (173).

The reactive dilation which follows the initial constriction on immersion of the finger in cold water is enhanced by combining the cold with a period of arterial occlusion for 5 min. (174). However, neither histamine nor acetylcholine injected intra-arterially advance the onset of the reactive dilation (175); possibly, the initial constriction may prevent the injected substances from reaching the vessels involved in this reaction. The reactive dilation still occurs during local anesthesia (176). These data may explain Blaisdell's observation (177) that this reaction to cold is a specific local phenomenon not wholly determined by the thermal state of the body. Smith (178) found that the constriction of isolated carotid arteries was a function of the rate of cooling rather than of the actual temperature. One notes also in his paper that the responses of these cooled vessels to epinephrine and acetylcholine are greatly prolonged at a low temperature. A longer life of the chemical mediator might intensify the constrictor effect of the vasomotor impulse traffic. This possibility should be kept in mind when employing the term "vasomotor tone" in reference to the peripheral vascular effects of cold. Heidelmann (179) has used the recovery of finger temperature after placing the hand in water at 15°C. as a measure of arterial tone.

The paresthesias elicited by immersing a limb in cold water were reported by Marshall (180) as being separate from those occurring with ischemia. However, Blaisdell's detailed studies (181) on the hand appeared

to relate pain and temperature sensations to the complex vascular sequence which is elicited by local cold. The changes in capillary resistance which may be noted in rats subjected to cold stress have been considered as part of a nonspecific stress syndrome (182). The decrease in circulating plasma volume (about 12 per cent) in the hypothermic dog and the accompanying increase in hematocrit was attributed to a possible trapping of plasma by vasoconstriction (183).

Muscular performance.—Reduction in the mobility of joints and an awkward slowing of movements are common experiences when living outdoors in a cold climate. Hunter *et al.* (184) attribute this to increase in the viscosity of synovial fluid with the fall in its temperature (185) so that the rate of shear in the fluid during the sliding motion in the joint diminishes; the frictional effect increases with decrease in rate of shear; hence, increasing fractions of the applied muscular force become ineffective in moving the joint. The early reduction in digital blood flow in the cold probably correlates in time with one's subjective experience of increasing awkwardness in movement. Analytical studies of the manual performance of a standardized task (186) indeed confirm this common impression, showing that the performance decrement parallels the drop in digital skin temperature, being less in persons whose fingers cool less. Skin temperature and two-point tactile discrimination exhibit the same inverse relation (187). Following this lead, the ingestion of a moderate quantity of alcohol should improve manual performance in the cold by dilating the peripheral blood vessels. However, actual testing of this idea led to some unexplained reversals in the relation between skin temperature and manual performance (188). The direct control of the blood vessels of joint tissues either by vasomotor nerves or drugs seems to have little effect on joint temperature although ice-packs placed over a joint do reduce its temperature (189, 190). Since manual skill may determine survival in the cold, one may speculate on the nice distinction which must be made at times between effects on total heat loss and on manual performance having possibly equal survival value. The reader will find the review on joints by Selle & Mason (191) pertinent to the understanding of thermal effects on joint mobility.

Cold adaptation.—Adaptation to cold is characterized by less discomfort, warmer extremities, and less shivering when exposed to cold. These differences are a matter of common knowledge, often the subject of interesting conversation. Analytical studies (192) show that it takes about fourteen daily exposures of from 16 to 18 hr. to effect full adaptation during which skin and body temperature patterns alter when the subject is exposed to cold; the final result is a warmer extremity in the cold-adapted subject. Possibly a general improvement in the coordination of autonomic activities may proceed in this type of adaptation as Mies (193) has suggested occurs in physical training. One may infer that the warmer extremity results from increased blood flow which Brown *et al.* (194, 195, 196) found to be the case in the hand and forearm of the Eskimo. These changes in blood flow alter the

peripheral tissue temperature gradients so that, although surface temperatures are higher on the bared hand and forearm of the Eskimo, the deep forearm temperatures are lower than in the nonadapted person exposed to the same ambient temperatures. As a result, the Eskimo may expose his skin to extreme cold without pain although his cutaneous pain thresholds are not significantly different (197); one may wonder if this would hold also if "cold" radiation were used to test thresholds to pain.

Both blood volume and basal metabolic rate are elevated in the Eskimo (196, 198) which is attributed by Rodahl (199, 200) to adaptation rather than to racial differences. However, the statistical study of Roberts (201) seems to show an inverse relation between mean body weight and mean environmental temperature. The warmer extremity of the cold-adapted person is probably attributable to decreased impulse traffic in the vasoconstrictor fibers. This could be caused by decreased sensitivity of the cold receptors, altered balance between the discharges of the cold and warm fibers whose temperature-frequency curves overlap, "conditioning" of the vasomotor reflexes involved, or altered balance between the hypothalamic centers controlling heat loss and heat conservation as a result of their unequally changed metabolic rates under the influence of heightened activity of the thyroid. These are unresolved questions.

Animal studies have contributed important information on the process of cold adaptation. Although metabolic adaptation is clearly demonstrated as part of the process of climatic adaptation in arctic and tropical poikilotherms, the selection of a suitable microclimate by the animal is also an important factor (202). Man attains the same objective with clothing and housing. Wild deer mice captured in the winter show a greater resistance to cold than those captured in the summer (203); part of the difference is because of a denser pelage. Dyeing the fur black in white mice increases their oxygen consumption in the cold, possibly as a result of greater radiative heat loss (204). Cold acclimation greatly increases the resistance of rabbits and rats to cold injury (205). Fregly (206, 207) demonstrated that the colonic and cutaneous temperatures of cold-adapted rats fell more slowly during a standardized exposure to cold than do those of control rats. He attributed this difference to higher heat production rather than to better insulation. The process of cold adaptation interferes with altitude acclimatization and the latter decreases cold tolerance below that of control rats. This may be considered as an instance in which adaptation to one stress interferes with adaptation to another. Fregly has referred to the phenomenon as negative cross-acclimatization. Further information on this topic is available in papers by Flückiger & Verzár (208, 209). Even peripheral nerves exhibit cold acclimatization; the gull's metatarsal nerve conducted at lower temperatures than nerve from the tibial portion; this difference was reduced or eliminated by the bird's wading in warm water (210). Tissue respiratory studies in the rat demonstrate increased visceral metabolism in cold-adapted rats (211) but the reverse in altitude-acclimated rats (212); the same implications ap-

pear in the decreased resistance of cold-adapted rats to whole body radiation (213), in the inhibition of restraint hypothermia by cold acclimation (214), and in the later onset of shivering (215).

A significant role of the thyroid in cold acclimation may be inferred from the following data. The thyroid gland of the guinea pig increases progressively in size for four weeks during chronic exposure to cold (215, 215a) which decreases the level of plasma protein-bound iodine in the rat (216, 217), elicits considerable loss of colloid (218), and increases the turn-over of I^{131} (219, 220). The oxygen consumption of albino rats diminished progressively from a winter level of from 690 to 712 to a summer level of from 660 to 680 kcal. per sq. m. per 24 hr. (221); caudal hypothalamic lesions reduced oxygen consumption but not thyroid activity. These effects were attributed to the rate of secretion of epinephrine (222). Seasonal variations in the reactivity of carotid arteries to epinephrine, acetylcholine, and histamine were duplicated by thyroidectomy (223). Drugs which depress oxygen consumption prevent its rise in rats exposed to a cooler environment (224).

There is evidence of the participation of the pituitary-adrenal axis in both cold and heat stress. Eosinopenia occurs shortly after exposure to cold but disappears within 24 hr. to be followed after 48 hr. by a slight eosinophilia which increases over a period of days (225). The eosinophil response to cold stress may be blocked by Dibenamine analogues which may influence the release of ACTH or the action of epinephrine (226). The diurnal rhythm in eosinophils is continued in mice exposed to 3°C. although at a lower level (227). The admittedly nonspecific character of the eosinophil response prohibits speculation on its significance in thermal stress. Cortisone increased the survival of mice exposed to cold which in turn reduced the toxicity of cortisone (228). It also protected adrenalectomized rats against cold for which they have low tolerance (229). Cold results in a decrease in the concentration of cholesterol and ascorbic acid in the adrenal gland (230); administration of glucose inhibited this response (231). Although large doses of ascorbic acid (325 mg.) increased the resistance of monkeys to cold (232), supplements of this vitamin to normal diets had no measurable effect on the cold tolerance of men but did increase their resistance when they were on survival rations (only 550 kcal. per day) (233). Increased urinary excretion of ascorbic acid (234), dihydroascorbic acid, and diketogluconic acids by rats during exposure to cold (235) may be caused by increased liver activity. Acclimation to cold has been reported to increase salt tolerance (daily doses of 50 to 60 gm.) (236). Urinary nonprotein nitrogen and potassium increased in control rats as well as in adrenalectomized rats (treated with cortex extract) during cold exposure (237), which may imply extra-adrenal factors in the control of these items.

Cold injury.—This subject has been discussed at length in two separate Macy conferences (238, 239). Field data on cold injury incurred by troops in the Korean campaign are presented in detail by Schuman (240) and Orr & Fainer (241). Experimental immersion foot has been reviewed recently by

Montgomery (242), who has published additional data on tissue oxygen tension during this condition (243). Meryman & Moore (244) described an ingenious application of radar to the detection and measurement of freezing in tissues. Recent reports on anticoagulant therapy in frost bite are not favorable (245, 246). Rutin was ineffective (247). There is evidence that heparin damages the walls of blood vessels (248).

Nutrition and climate.—A recent symposium on nutrition under climatic stress disposes of the need for a detailed consideration of this topic in this review (249). A few additional items may be mentioned. The food consumption of rats exposed to cold is regulated, as one might expect, according to its caloric value rather than its composition (250). The cold-acclimated rat shows persistent reduction in the glycogen levels of the liver, diaphragm, and heart but not in those of skeletal muscle (251). At the same time, blood lactate does not increase (252). Deposition of skin fat parallels a general increase in body fat (253); there does not appear to be any specific effect of the environmental temperature on fat distribution; therefore, a high fat diet, although favorable towards increased insulation against the cold, would be so only in relation to its caloric level. The cold-exposed rat seems to require increased intakes of thiamine, riboflavin, pyridoxine, ascorbic acid, pantothenic acid, and vitamin B_{12} (254, 255). Vitamin supplementation for men living in a cold environment is being studied intensively in the Army Medical Nutrition Laboratory at Denver (256). The supplemented group showed less fall in rectal temperature when exposed to cold at rest, although there seemed to be no effect of vitamin supplementation on their performance in various exercise tests.

Nervous Mechanisms

Nervous regulation of body temperature must be initiated either directly by some particular temperature acting on some particular thermosensitive mechanism or indirectly through nonspecific effects, such as changes in metabolic rates. Although hypothalamic lesions may result in gross changes in tolerance for heat or cold or both, Forster & Ferguson (257) observed only small fluctuations in the hypothalamic temperature of the unanesthetized cat; they also noted its relative independence of environmental temperature, the lack of correlation between peripheral vasomotor tone and hypothalamic temperature, and the latter's instability under anesthesia. Stoner & Shapiro (258) applied diathermy to the head and observed marked peripheral vasodilation which could not be elicited in a cold room; rectal and oral temperatures were unaffected. Carlson (259) approached the problem of the adequate stimulus for shivering through a comprehensive evaluation of the transitional thermal state of the subject by means of measurements of skin and rectal temperatures, regional heat loss (Hatfield tellurium discs), heat production, and digital blood flow. He observed the following sequence of events: skin cooling, reduced finger blood flow, shivering, increased oxygen uptake. The relation of shivering to rectal temperature

varied; so also did the cutaneous thresholds. The results may be summarized in the general statement that shivering depends on the total thermal state and may appear when either skin or deep temperatures fall low enough. Cooling of the upper respiratory passages or trachea also may elicit shivering in the lightly anesthetized piglet (260); this effect which may result in brief episodes of shivering on inspiration is probably of sensory origin since vagotomy abolishes it. Hemingway & French (261) concluded from immersion experiments on rhizotomized (L_1-S_2) dogs that the "central" mechanism is quite insensitive to changes in its temperature and that the cutaneous thermal receptors exert a "fine" reflex control of peripheral vasomotor tone. This may be true for transient states. Zotterman's able review (262) on the warm and cold receptors should be consulted in this connection. Additional data are available in papers by Dodt *et al.* (263) on the role of acetylcholine in their discharges, on the differential thermosensitivity of mammalian A-fibers (264), and by Hensel (265) on the time factor in thermoreceptor excitation and on thermal receptors in insects (266, 267). Woodcock (268) has applied the theory of heat exchange to the common impression that damp cold air is more disagreeable than dry air at the same temperature; this effect is real and is most noticeable near the freezing point, disappearing when conditions favor the evaporation of water.

Central mechanisms.—Keller *et al.* (269) have studied the posterior hypothalamic gray in experiments in which this region was coagulated by heat; the resultant dog preparations were poikilothermic only against cold, and still regulated well against heat, but, unfortunately for experimental purposes, exhibited rage all too readily. Such a preparation would otherwise have considerable advantages for experimentation. McCrum (270) concluded that, in the cat, hypothalamic mechanisms controlling heat loss and production are intermingled diffusely in the anterior hypothalamus and preoptic area, and that the relative density of each varies among individuals. In a later study on the rat (271), he and his colleagues placed bilateral electrolytic lesions which interfered with regulation against cold when located in a horseshoe-like area extending from the superior border of the posterior surface of the optic chiasm to the ventral surface of the thalamus, thence caudally dorsal and lateral to the mammillary bodies. Lesions in this area must be bilateral in order to destroy regulation against cold. Their data do not confirm earlier emphasis on the area surrounding the walls of the third ventricle, on the anterior hypothalamic nucleus, or on the medial areas of the hypothalamus as sites for regulation against cold. Hemingway *et al.* (272) were able to suppress shivering by stimulating certain points within the hypothalamus and midbrain; the most sensitive region was the preoptic of the hypothalamus; they think that this suppressor mechanism operates when there is need for coordinated somatic movements during shivering. Certainly, common experience indicates that some such mechanism is available.

Certain data on man are pertinent to this review. When skin temperatures are measured within a narrow zone, they begin to show variability

within this zone after the first postnatal week; this variability increases with the appearance of sweating, particularly in the palm where it is greatest (273). This phenomenon may represent the activation of peripheral sudomotor and vasomotor mechanisms. The psychogalvanic skin response may be "conditioned" in the classical sense (274). This observation may be coupled advantageously with that of Eccles & McIntyre (275) who showed that increase in synaptic usage seemed to enhance the function of normal synapses, at least in monosynaptic spinal reflex arcs. Such a mechanism if available could go a long ways in accounting for acclimation to either heat or cold. A mesencephalic lesion, involving bilaterally the tegmental area in the midbrain and anterior pons, was associated with a hypothermia of unusual duration and extent (276). Shivering was not apparent; evidence for peripheral vasoconstriction appeared only in the upper extremity, the lower extremity being quite warm. Hyperthermic reactions may develop during hot weather in cases of Parkinsonism, particularly as the result of atropine-like drugs (277); these cases present other evidence of hypothalamic disturbances. Wide distribution of the sudomotor and vasomotor fibers in the anterolateral columns was inferred from the results of anterolateral chordotomy on the topographical distribution of thermoregulatory sweating (278). Studies on the course of these fibers through the sympathetic trunk and the regional topography of their distribution (279) may bear on the topographical sequence in sudomotor and vasomotor responses servicing temperature regulation.

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RESPIRATION[1,2]

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The last year's harvest has been bountiful. Particularly impressive is the fact that many of our current studies of normal physiology of respiration stem from clinical laboratories. In view of the considerable contributions forth-coming in this field, it is not surprising that on both sides of the Atlantic warnings have been specifically directed to the respiratory physiologist. Cara (33) believes that a physician cannot think about respiratory problems in the same physical terms as a physiologist who has been trained as a Ph.D. More specifically he states that the physics of respiration has to be considered from a physician's point of view, implying two laws of physics, one for healthy individuals and Ph.D.'s, the other law for those with pulmonary dysfunction and M.D.'s. He thus questions the mechanics of respiration as put forward by Fenn and attempts to solve this problem by new laws. On this side of the Atlantic, Rappaport (150) addresses himself to the modern respiratory physiologists who have embraced mechanistic concepts. A review of the recent literature convinces him that they have been seduced by the science of physics and that a vitalistic approach into the realm of "visceral lung function" would be more rewarding.

Books and Reviews

Over the last year there have appeared a number of reviews and books of interest to the lung physiologist. Hayek (76) presented an excellently illustrated book on the anatomy of the lung which has been written not for the anatomist but for the physiologist, pathologist, and clinician. Brown (28) reviewed the general physiological effects of hyperventilation while Sjöstrand (166) discussed the distribution of blood within the thorax. The problem of respiratory reflexes arising from the lung and the chest has been presented in a monograph by Bucher (29). Dawes & Comroe (45) have accomplished an amazing order and clarity in their sifting from a deluge of pharmacological observations the effects of various agents acting upon chemical receptors in the heart and lung. Lilienthal & Riley's (105) most excellent review of respiratory clinical problems has been directed toward the normal and ab-

[1] This review covers the period from approximately July, 1953 to June, 1954. It was not possible to include even the majority of titles reviewed, and many important contributions as well as all abstracts were omitted.

[2] The following abbreviations are used in this review: A-a (alveolar-arterial difference); PAP (pulmonary artery pressure). Symbols used conform to recommendations published in *Federation Proceedings* **9**, 602 (1950).

[3] It is a pleasure to acknowledge the technical assistance of Mary-Alice Breckenridge.

normal physiology of pulmonary blood flow as well as toward the problem of gas diffusion in the lung. The reader is also directed to a review of the comparative physiology of respiration which has been brought together in this volume by Zeuthen (193). Cara (33) and Sadoul (157) have each presented a monograph dealing with clinical problems and the newer concepts of lung function tests, including spirography, bronchospirometry, and the mechanics of respiration. Fleisch's (55) beautifully edited monograph covers the methods and apparatus which he has developed over the last decades for recording the various aspects of lung function. It seems to the reviewer that his metabograph is a crowning achievement. This instrument will record directly on paper the tidal volume, the total ventilation (BTPS), the oxygen consumption, as well as the CO_2 output (STPD), and the respiratory quotient. The nature of the subject of Karpovich's book is well expressed by its title, *Adventures in Artificial Respiration* (87).

Alveolar Gas Exchange

Normal fluctuations in alveolar gas composition.—With the increasing interest devoted to the composition of alveolar gas it is not surprising to find more and more evidence revealing a cyclic nature not only of the alveolar gas concentrations but also of the sensitivity of the respiratory center. Many types of cyclic phenomena can now be recognized. Chilton, Barth & Stacy (39) have presented a detailed theoretical analysis of changes occurring during a single respiratory cycle. Peak differences of 3.6 and 2.9 mm. for O_2 and CO_2 respectively are predicted and agree well with those of DuBois. Such differences must be superimposed upon larger cycles occurring at minute intervals or longer, as revealed by continuous changes in the exchange ratio (53) which probably reflect similar cyclic changes in ventilation or cardiac output or both. Such cycles are in turn superimposed upon diurnal rhythms. Mills (127) reports a rising CO_2 tension at night, and during natural, deep sleep he found CO_2 tensions as high as 54 mm. Koepchen *et al.* (91) have shown by CO_2 breathing tests that not only the CO_2 threshold but the sensitivity undergoes diurnal changes. The response curve is shifted to the left during the day. Finally we can add another cycle in the human female where changes in CO_2 threshold and sensitivity are correlated with the menstrual cycle as previously shown by Loeschcke. Goodland & Pommerenke (70) have corroborated these findings of a premenstrual fall in CO_2 tension presumably associated with the luteal phase. During pregnancy it remains low and rises sharply post partum (71). Injections of adrenocorticotropic hormone (91) as well as of cortisone (92) and desoxycorticosterone (13) produce slight shifts in the CO_2 ventilation response and threshold.

During the unsteady state the large changes in gas exchange ratio are well recognized and are largely attributable to the changes in CO_2 stores of the body. The magnitude of these potential CO_2 stores have been determined by Freeman & Fenn (61). The adult rat has on the average 1.85 cc. CO_2/gm. of body weight, 83 per cent in the bones and the rest distributed throughout

the soft tissues of the body. It is this latter quantity presumably that can be easily added to or subtracted from during the so-called unsteady state. However, by chronically lowering the alveolar CO_2 in these animals 80 per cent of the total CO_2 lost came from the bones while with chronic increase of alveolar CO_2 32 per cent of the over-all CO_2 store gain went into the skeleton. Extreme difference in the exchange ratio can also be observed when two lungs inhale simultaneously different O_2 mixtures. The resulting alveolar O_2 differences not only effect the relative O_2 uptake of each lung but also effect the unloading of CO_2 (147).

Alveolar-arterial gas differences.—Bartels recently devised a potentiometric method for the estimation of O_2 tension in whole blood of man and has now presented his results (9, 10) of the A-a O_2 difference in 54 healthy men with alveolar O_2 tensions ranging from 30 to 500 mm. These experiments are of considerable interest because they show a single method applied over a large range of O_2 tensions. Below alveolar O_2 tensions of 107 the A-a difference remains approximately constant at 5 mm. while above this value it rapidly rises and plateaus off at 30 mm. To account for these observations a discussion of the diffusion and shunting factors is given by these authors and Opitz (138). Filley *et al.* (53) and Björk *et al.* (20) have been concerned with technical improvements of the Riley technique for arterial oxygen tensions. Filley *et al.* believe that the indirect approach for determining the alveolar oxygen is open to some question since at rest the expiratory exchange ratio varies from moment to moment. During exercise these variations are minimized yielding, therefore, more reliable indirect alveolar values. In their hands the normal A-a gradient is approximately 10 mm. and doubles with exercise.

Tomashefski, Chinn & Clark (181) have presented evidence for an "apparent" CO_2 gradient between the capillary blood and the alveolar air produced by the intravenous injection of rather large doses of a carbonic anhydrase inhibitor (2-acetylamino-1,3,4-thiadiazole-5-sulfonamide; Diamox) in dogs. Their experiments suggest that during the transit of blood through the alveolar capillary there is not sufficient time to unload the CO_2 from the red cell but only from the plasma, resulting in red cell-plasma CO_2 differences of 20 to 30 mm. The plasma is assumed to be in equilibrium with the alveolar CO_2. However, during the arterial CO_2 determination by the Riley method there is sufficient time to obtain equilibrium between the cells and plasma resulting in an arterial CO_2 very much larger than that of the alveolar air. Becker, Hodler & Fishman (15) were unable to demonstrate such differences in man when they administered smaller doses of Diamox by mouth.

The normal A-a differences for O_2 and CO_2 in the dog have been determined by Suskind (174). Compared to man they are quite large but breathing low O_2 become reduced to 5 mm. When pulmonary edema is induced by 1-(1-naphthyl)-2-thiourea (ANTU), Williams (190) showed that the A-a O_2 difference became considerably smaller when low O_2 was inspired instead of air, indicating that the anoxemia of edema is attributable to complete ob-

struction of some airways producing a large venous admixture while other airways remain open with little impaired diffusion.

Unequal distribution of ventilation and lung perfusion.—Bates *et al.* (12) have tried to evaluate the uniformity of alveolar ventilation at various lung volumes by the rate of pulmonary nitrogen clearance breathing He-O_2 mixtures. The clearance curves were resolved into under-ventilated portions (75 per cent) and over-ventilated portions (25 per cent). These fractions remained constant at all lung volumes, suggesting that the observed distribution occurring during a single breath is time dependent and not volume dependent. Tackling the problem of uneven ventilation in a more direct manner, Martin *et al.* (115) sampled alveolar gas simultaneously in man's right upper and lower lobe. In the upright position the exchange ratio is larger in the upper lobe, while in the supine and head-down position the ratio is the same. Later experiments indicate that these differences do not depend upon the resting lung volumes (116). These findings are of considerable interest since they allow the first indication by direct sampling that the alveolar composition is not necessarily uniform in different lobes and indicates a larger alveolar ventilation-perfusion ratio in the upper lobes while standing. Unfortunately we are dealing here with a difference in ratio and thus are unable to predict whether the upper lobe is relatively over ventilated or under perfused. Direct measurements of lobar ventilation are required to give us this answer. In this connection it is of interest to consider the experiments of Inada *et al.* (83) who tested by broncho-spirometry the oxygen uptake and ventilation of each lung in 10 normal men in the left and right lateral position as well as supine. From these observations one may calculate that in the supine position the ventilation-perfusion ratio is nearly the same in both lungs, as might be expected. However, in either lateral position proportionally more blood than ventilation is shifted to the down lobe. If air is breathed one would calculate a 10 mm. O_2 difference between each lung. These last two studies indicate that gravity can shift independently the ventilation-perfusion ratio within the subdivisions of the lung and that the concept of equal ventilation-perfusion ratio in all parts required by the hypothesis of homeostasis is not necessarily correct.

Respiratory dead space.—The nonrespiratory physiologist may consider the various attempts over the last 50 years to measure the dead space analogous to constructing better mouse traps. However, the major gain has not been so much in the more precise measurement of this quantity as in a clearer concept of the complexities of alveolar gas composition. Rossier *et al.* (155) have presented a review of the current methods employed. The novel approach of Pappenheimer to the dead space problem has been continued by Fishman (54) who applied the "isosaturation" technique in man. The dead space remains constant over a wide range of breathing frequencies as well as during light exercise. This method theoretically measures the "anatomical" dead space and is distinct from the "physiological dead space" obtained by determination of arterial or alveolar gas concentrations. What

part diffusion plays in the determination of the dead space has been very elegantly pursued with a mass spectrometer which records the changing gas tension during a single expiration for gases such as O_2, CO_2, N_2, and He (11). With breathholding the dead space is decreased at approximately the same rate for all gases. This reduction in dead space is ascribed to "the churning action of the heart" so that relative diffusion differences are minimized.

Diffusion.—Riley and associates (152) have shown with the "low oxygen method" that the diffusion capacity of the lungs can be varied with different work loads of the treadmill. The diffusion capacity increased rather suddenly at oxygen uptakes of approximately 1200 cc./min. With larger work loads no further increase was observed. This maximum diffusion capacity is approximately 65 to 70. Of particular interest are the facts that (*a*) beyond this critical value of approximately three to four times the resting metabolic rate the body has no means for increasing the diffusion capacity and (*b*) that the rather sudden change from a moderate to the maximal diffusion capacity signals a sudden opening up of hitherto closed pulmonary capillaries. Filley, MacIntosh & Wright (52) have developed and improved Krogh's method for determination of the diffusion capacity of CO and obtain a value of 17 in normal resting subjects. They observe also the attainment of a maximal diffusion capacity at about four times the resting O_2 uptake. Their average value is 36. These values are comparable to those of Riley's when multiplied by 1.25 (Graham-Exner's Law). When the maximal diffusion capacity is tested in man of various ages (17 to 76 years) a negative correlation with age results, indicating roughly a loss of five units for each 10 years of life and suggests an equivalent loss in pulmonary capillary area (42).

The results of *in vitro* experiments on the diffusion of O_2 into various concentrations of protein solutions are given in an excellent monograph by Kreuzer (93). Applying his diffusion constants to physiological conditions he finds that diffusion alone may not be sufficient to explain the O_2 transfer across the alveolar membrane. A stimualting analysis of the gas exchange across the five tissue layer placenta of the sheep fetus is presented by Barron & Alexander (8). The maternal and fetal blood stream move in opposite directions and maintain a mean O_2 difference of 37 to 48 mm. along the capillary. Estimation of the O_2 diffusion capacity of this tissue is 0.006 at 56 days and increases to .27 near term.

The alveolar membrane.—Although under normal circumstances the alveolar membrane is of little consequence as a diffusion barrier its intimate structure is still being investigated by the light (176) and electron (175, 109) microscope. Some structures seem to be present and evidence for a nucleated alveolar epithelium is given (109). Macklin (112) speculates about the function of a mucoid film which is continuously secreted and removed. Since it is supported by the alveolar epithelium he believes that it serves to protect and cleanse the diffusing surfaces. A stimulating analysis of the internal surface area changes during the growth of the human lung is presented by

Short (163). The lung surface/body weight ratio remains constant from the later months of the fetus to adult life.

Breathholding.—It has been long appreciated that during the process of altitude acclimatization the breathholding time on air is gradually diminished. The loss of alkali reserve which parallels this gradual decrease has been held responsible for this phenomenon. However, Stroud (172) has shown that man at sea level does not respond in a similar fashion when an equivalent loss in alkali reserve is produced by the ingestion of ammonium chloride. His conclusions lead to the assumption that the decreased breathholding time at altitude is primarily associated with an increased sensitivity to CO_2, per se. Two important papers have contributed to a revised concept of the breathholding breaking point. Both Mithoefer *et al.* (128) and Fowler (60) have clearly shown that the breaking point is not only a function of the O_2 and CO_2 tension. In an elegant series of experiments Mithoefer showed that when gases at various O_2 tensions are breathed the lung volume, per se, contributes to the breaking point as measured by his special technique. For example, at the same alveolar P_{O_2} of 200 mm. the P_{CO_2} at the breaking point could vary from 38 to 78 Min. depending upon the volume of the lung. Large volumes were associated with high breaking points and vice versa. Fowler tackled this problem by having his subjects rebreath an 8 per cent O_2 and 7.5 per cent CO_2 mixture after a maximum effort of breathholding. The relief was instantaneous, enabling the subject to resume breathholding for a shorter period. This maneuver could be repeated twice despite progressive decrease in the hemoglobin saturation and increasing CO_2 tension. Binet *et al.* (17) observed that the breaking point CO_2 value before and after previous hyperventilation was different. These various experiments indicate that in the future certain reservations have to be made in the interpretation of the breaking point based on O_2 and CO_2 alone.

Reduced barometric pressure.—Acclimatization of man to high altitudes continues to draw interest in various parts of the world. Winterstein (191) exposed 19 subjects to an altitude of 1850 m. (6,000 feet) in the mountains of Turkey and observed an average fall of 5 mm. alveolar CO_2. He is much concerned with this observation since the change in total ventilation as well as CO_2 output is insufficient to account for this reduction. Unfortunately, he does not compute the altered alveolar ventilation, which might explain his results, but makes an increased CO_2 diffusion responsible, facilitated by the lowered barometric pressure. This ignores the fact that the final step in the CO_2 transport is not diffusion but alveolar ventilation. If air rarefaction of 150 mm. Hg facilitates CO_2 diffusion it should certainly be impeded by compression to 2100 mm. Hg. But this latter pressure does not raise the alveolar P_{CO_2} as Haldane and more recently Lambertsen *et al.* (94) have shown. Åstrand (2), with one subject, has confirmed the work of previous investigators that after acclimatization of five days at an altitude of (4000 m. (P_B=462) the acute exposure to oxygen has a barely significant effect upon the resting alveolar ventilation. As he and others (40, 149) have recently

shown again, the alveolar P_{CO_2} rises only 1 mm. or so but never returns to the sea level value, for which an additional 8 to 10 mm. are required. Whether or not this is to be interpreted as resulting from a change in chemoreceptor activity after altitude acclimatization is a much more difficult question since the observed changes in action potential frequency of the carotid body nerves in anesthetized, hypoxic cats (3) are certainly no guarantee for an equivalent change in the alveolar ventilation in unanesthetized man. It is well appreciated from the older literature that increased or decreased chemoreceptor activity is not necessarily synonymous with increased or decreased alveolar ventilation under these conditions, and we must differentiate between chemoreflex drive and chemoreceptor activity. Therefore, the physiological blocking of chemoreceptors with oxygen breathing after altitude acclimatization suggests a largely centrogenic breathing and a diminished hypoxic (chemoreflex) drive at rest. On the other hand, with exercise (up to 3 l. O_2/min.) Åstrand (2) was able to show after acclimatization large differences in ventilation and alveolar CO_2 when breathing air and O_2. Under these conditions enhanced chemoreflex drive is evident. In very carefully controlled experiments, Loeschcke (106) has tested the chemoreflex drive in 20 subjects where they were switched from air to 32 per cent O_2 and back again to air. The total ventilation with the higher O_2 was reduced by 8 per cent during the first minute with subsequent recovery over the next four minutes. The alveolar CO_2 increased by approximately 1 per cent. After consideration of the chemical changes in the blood and tissues attributable to the complete saturation of the hemoglobin, he suggests that the chemoreceptors are normally active while breathing air.

Rahn and associates (148, 149) exposed themselves for one week on two expeditions to an altitude of 14,000 feet (4300 m., $P_B = 456$). They concluded from their breathholding experiments and from breathing CO_2 in O_2 mixtures that the response to CO_2 is definitely increased but that an altered O_2 sentivity is absent. On the other hand, Chiodi *et al.* (40) believed to have demonstrated that long time residents in the Andes at elevations of 14,000 feet slowly regain their sea level sensitivity to CO_2. Beard, Bell & Howell (14) reported some technically remarkable experiments of acclimatization carried out on 10 dogs which were exposed continuously for 7 to 15 weeks in an altitude chamber at a simulated altitude of 20,000 feet ($P_B = 350$). Their acclimatization may be judged by the increase in the hematocrit which rose from 44 to 75. After such acclimatization the animals were returned to ground level for 1 hr. and were then anesthetized in order to test their pulmonary vascular and ventilation response to a mixture of 8.5 per cent oxygen which yields the same inspired tension they had at altitude. Under these conditions the total ventilation increased approximately 50 per cent. These experiments, as well as those of Åstrand (3) on partially acclimatized cats, suggest that these animals maintain a considerable chemoreflex drive and respond differently from man after acclimatization. However, it should be kept in mind that in both of these instances the animals were anesthetized

and that this disrupts the normal balance between the chemoreflex and the centrogenic drive.

High barometric pressure.—An excellent analysis of the problem of gas exchange in man at high atmospheric pressure has been presented by Lambertsen and associates (94) who provide an explanation for the 25 per cent increase in ventilation associated with exposures to 3 atm. O_2. The internal jugular venous P_{CO_2} increased 2 or 3 mm. as a result of the nonreduction of hemoglobin. This in turn produces a hyperpnea which not only lowers the arterial P_{CO_2} but also reduces the cerebral blood flow 16 to 23 per cent and thus maintains an increased cerebral arterio-venous CO_2 difference. It seems from these observations that CO_2 retention, per se, cannot account for oxygen poisoning effects at high pressures until pulmonary damage is first encountered. Bahnson & Matthews (5) and Lambertsen *et al.* (95) exposed man and animals to various O_2 pressures. Their work indicates that the CO_2 tension of gas depots in the body may rise to extremely high values but only after pulmonary damage has first been produced.

Regulation of Respiration

Chemical regulation.—While it is convenient to consider the arterial blood CO_2 tension as a respiratory stimulus, increasing evidence tends to focus on the venous or tissue CO_2. The careful experiments of Lambertsen and associates (94) indicate that the internal jugular venous CO_2 tension is much better correlated with the ventilatory response during CO_2 breathing than is the arterial P_{CO_2}. Leusen (101) has tackled this problem by direct perfusion of the cerebral ventricles. With the use of various buffer agents he was able to vary independently the pH, HCO_3^-, and the CO_2 tension (102). Intraventricular alteration of H^+ independently of the CO_2 and HCO_3^- does not influence the respiratory activity, but the CO_2/HCO_3^- ratio is important. Respiration is more depressed with higher total buffer concentration. Tenney (178) has determined the sensitivity of the respiratory center (breathing CO_2) in patients with emphysema and relates their response to the CO_2 content of their blood. When these data are compared with similar values reported for chronically hyperventilated subjects, one obtains a correlation indicating that the sensitivity index varies inversely with the CO_2 buffer content of the blood. When simultaneously the pH of the blood and cerebral spinal fluid are recorded after CO_2 breathing and hyperventilation the ventilation follows the changes in the latter (103). Winterstein (192) has modified his reaction theory so that the respiratory center is controlled by the chemoreflex drive or the cerebral spinal fluid composition which in turn is influenced by the blood/cerebral spinal fluid barrier.

Alteration of the gasp reflex has been employed by various authors to study the changes of the respiratory center (64, 137, 156). The changes in the CO_2/ventilation response curve produced by morphine and meperidine in normal men has been presented in excellent fashion by Loeschcke *et al.* (107).

Nervous regulation.—The concept that the respiratory center of the medulla is by itself nonperiodic and thus incapable in the absence of extramedullary factors of producing rhythmic breathing continues to be challenged by Breckenridge & Hoff (27). They observed that apneusis does not appear under certain conditions but when present can be abolished by progressive anoxia which re-establishes rhythmic breathing. Apneusis is considered only as an overlay of inspiratory tonus, akin to decerebrate rigidity, arising from the apneustic center. The function of the latter is to prevent apneusis or respiratory hypertonus but is in no way responsible for the respiratory rhythm. On the other hand, Kerr and associates (89, 90) suggest that normal apnea is generated by a supra-medullary vagal complex which in turn drives the respiratory center. Sustained afferent vagal stimulation after apneusis produces rhythmic respiration for the duration of stimulation. Their concept (90) would ascribe to the normal vagal afferent activity a dual excitatory as well as inhibitory action rather than a repetitive inhibition alone as Pitts suggested.

Respiratory reflexes.—A survey of the various respiratory reflexes arising within the lung and chest is given in the monograph by Bucher (29), while the chemoreflexes within the thorax have received specific attention in the review by Dawes & Comroe (45). The proprioreceptive respiratory reflexes of Fleisch seem to be a recording artifact for they can be reproduced in dead animals (151). By stimulation of the central vagus stump with high and low frequencies Josenhans (85, 86) can simulate the action of the inflation and deflation fibers respectively. Taugner *et al.* (177) recorded not only the contractions of the diaphragm representing the inspiratory tone but also those of the isolated belly muscles which express the expiratory tone. With changing lung volumes they show that the tonic actions of these two muscles are reciprocal. In man, during bronchospirometry, the occlusion of one bronchus at the end of expiration leads to an immediate increase in the contralateral tidal volume and frequency of breathing. The opposite responses are obtained when the occlusion is made at full inspiration. These responses are explained by the excitation of the two types of stretch receptors (146).

By progressive cooling of the vagus nerve Widdicombe has analyzed three different receptors responding to lung inflation (186): the Hering-Breuer inhibitory reflex, the excitatory reflex, and a new, short-acting, inhibitory reflex of the inspiratory activity which is only obtained by large lung volume inflation and is quite distinct from the Hering-Breuer reflex.

The conduction velocities in single respiratory stretch receptors fibers have been determined by Paintal (140). Widdicombe has presented a systematic analysis of the various receptors in the tracheal-bronchial tree which respond to inflation and has considered their adaptation rates (187). He has also dealt with the various reflexes from the same tract which produce coughing (188).

An excellent analysis of the "crossed phrenic" and "bilateral phrenic"

phenomenon has been presented by Dolivo (49). By recording the action potentials in the phrenic nerve he has shown an increase in the discharge as soon as the nervous conduction beyond this point is interrupted either in the whole phrenic nerve or in part of it. This increased activity is seen in an increased frequency as well as recruitment of new neurons during the next succeeding inspiration and ceases with the next inspiration when the block is removed. The two possible explanations for this phenomenon are the disappearance of inhibitory impulses arising from the diaphragm or excitability modifications of the motor neurons as soon as nerve conduction is interrupted in their axons.

The orthostatic respiratory reflex in guinea pigs is vagus dependent. With hypothermia below 23°C. the frequency response is still present but no longer dependent on vagal activity (182). The new born guinea pig, on the other hand, does not exhibit this adult pattern (72), which is gradually acquired after birth. Section of the olfactory tract in guinea pigs produces extinction of the respiratory reflex of olfactory origin which differs from reflexes aroused by trigeminal receptors. The former is abolished by body cooling to 27°C., the latter by cooling to 22°C. (124). As far as chemoreflexes are concerned it is only possible to list further work which appeared since the review of Dawes & Comroe (45). The largest number of observations concern themselves with 5-hydroxy-tryptamine (serotonin) (50, 69, 158, 159). This is partly destroyed by the isolated, perfused lung (63). The effects of papaverine (132), *p*-chlorophenyl-ethanolamine (80), and intravenously administered local anesthetics (194) are reported.

Contribution of the respiratory muscles.—Wade (185) was able to measure the linear displacement of various components of the chest during respiration by simultaneous tracking of the x-ray shadow of each dome of the diaphragm, recording a spirogram, and measuring the chest expansion as well as the vertical movement of the thoracic cage. Quiet respiration gave diaphragm movements of 1.5 cm. and chest circumference changes of 1.2 cm. when erect and 0.7 cm. supine. One-fourth of the vital capacity volume was attributable to chest expansion while $\frac{3}{4}$ was attributable to the diaphragm. No evidence for voluntary control over the diaphragm alone could be established. Jones, Beargie & Pauly (84) made electromyograph recordings of the intercostals and other respiratory muscles. Their general conclusions are that the intercostals supply only tension to keep the ribs at constant distances from each other while the chest is expanded from above by the scaleni and from below by the diaphragm. With chronic phrenectomy of rats Davis & Morris (44) were able to show a tremendous reduction in the minute volume. They consider the diaphragm the chief respiratory muscle in the rat. The contribution of the abdominal muscles to the act of expiration [Campbell & Green (31)], interpreted from electromyographic recordings, indicates high grade activity only during static pressure production. During involuntary breathing the activity of the abdominal muscles is relatively small. The intragastric pressure changes which accompany quiet respiration can be accounted for

by compression of the abdominal content by the diaphragm but not by abdominal muscle tone, per se (32). However, when the ventilation exceeds 70 l. per min. the respiratory pressure cycle in the stomach is reversed by the now actively contributing abdominal muscles of expiration.

Mechanics of Respiration

During the 1920's three classical studies heralded the birth of respiratory mechanics. Rohrer presented his fundamental concepts of ventilation mechanics, and v. Neergaard and Wirz showed the practical approach to the solution of the dynamic events employing the pneumotachograph which had just been described by Fleisch. During the next two decades these studies were largely forgotten, and it is only within the last few years that this field experienced a tremendous revival which in part can be ascribed to our recent advances in instrumentation. The modern worker in this field can be easily recognized from afar with an intra-esophageal balloon connection emerging from his nose and a modified Fleisch tachometer hanging from his mouth while a two channel oscillograph records respectively the changes in intrapleural pressure and the instantaneous air flow.

One of the chief difficulties has been a reliable method for the determination of the alveolar-mouth pressure difference during every phase of the respiratory cycle without resorting to intrapleural punctures. Mead & Whittenberger (121) have given an excellent critical evaluation of the interrupter method of Otis and the intra-esophageal balloon method. Although both have some shortcomings the latter is to be preferred, while Fry *et al.* (62) have tried to avoid these difficulties by combining both methods. Mead & Whittenberger (122) have also given an excellent description of the physical properties of the human lung. The average compliance of this organ during spontaneous breathing is 220 cc./cm. H_2O pressure difference. The resistance offered by the broncho-tracheal tree to an air flow of 1 l./sec. is approximately 2 cm. H_2O. The average constants in the Rohrer equation for streamlined and turbulent flow are 1.74 and 0.28 respectively. With small lung volume the resistance to air flow is about twice that found with maximum lung volume. When small lung volumes are reached after rapid expiration the resistance may increase dramatically 20-fold. This observation is of great interest in studies on emphysematous subjects to which Fry *et al.* (62) have devoted their attention. During expiration the pressure-flow curve rapidly flattens out as a result of the collapse of the unsupported bronchioles and offers striking evidence of the expiration difficulties encountered by these people.

McIlroy, Marshall & Christie (120) have analyzed the work of ventilating the lungs. Seventy per cent of it is expended on elastic work and 30 per cent on the nonelastic work of tissue deformation and air resistance. They proved in a very elegant fashion the predictions of Otis & Fenn that the minimal work for a given ventilation is associated with a particular frequency of breathing. The optimal frequency for minimal work with resting ventilations

varies in individuals from 6 to 15 per min. and is increased for larger ventilation volumes. Both emphysematous patients (119) and subjects with cardiac failure (114) breathe at frequencies associated with minimal work. While in both the total work of respiration is greater, particularly with exertion, in the former the increased work is largely attributable to changes in viscous resistance and in the latter to elastic changes of the lung. Noelpp-Eschenhagen *et al.* (133) have reported similar changes in patients with various forms of dyspnea.

Cara (33) has developed a theory of the mechanics of rib action and has approached the problem of viscance and elastance from a theoretical analysis of a time-forced expiration volume curve. This curve is explained as a summation of two exponential functions, one representing elastance and the other viscance (34). The resistance offered by the nasal passages during normal respiration has been measured by Stoksted (171). Static pressure-volume diagrams of isolated dog lungs (125) as well as artificial lung models (160) have been presented. The increased chest compliance observed after vagotomy has been ascribed to changes in muscle tone (183).

Coughing.—The physiology of coughing has received considerable attention. Barach *et al.* (6, 7) have increased the effectiveness of their exsufflator for artificial coughing in respirator patients by combining their old method with simultaneous negative pressure at the head. They are able to obtain explosive decompressions of the chest within 0.02 sec. with pressure differences of 60 to 80 mm. of Hg. Expiratory flow rates of 10 l./sec. can be achieved in man and as high as 20 l./sec. in the dog. Bickerman (16) has shown with this technique that in dogs radio-opaque solutions and foreign bodies such as safety pins can be ejected quickly from the bronchus. Pressman (144) has given an extremely lucid and well illustrated account of the action of the three sphincters of the human larynx and their role in raising the intrathoracic pressure such as precedes a cough. A most unusual discussion by Di Rienzo (48) describes coughing as a dynamic act of the bronchial mucosa which is able to transport air or secretions by quick peristaltic waves. His roentgenological analyses lead him to state that one coughs with the bronchi and not with the thorax. This concept is violently attacked by Stutz (173) who gives an excellent physical concept of the act of coughing with the bronchi playing only a passive role. Sharpey-Schafer (161) observes during intermittent coughing an elevated intrathoracic pressure which he attributes to the possibility of air trapped by reflex broncho-constriction.

Mechanical resuscitation.—For a general review of manual as well as mechanical methods the reader is referred to Karpovich's book (87). Collier & Affeldt (43) have applied the pressure-volume relationships of the chest in polio patients to the evaluation of chest respirators. The pressure-volume diagrams for each type of resuscitator indicates the cycling pressures that are required for adequate ventilation in order to maintain a normal alveolar CO_2. This type of study is very much needed because it seems that the polio patient is generally overventilated (4, 43). This, by itself, may not be harm-

ful, but one would anticipate difficulties in weaning patients from the respirator after the respiratory center has become acclimatized to a low P_{CO_2} and requires a larger than normal ventilation (28). In cases where it is not possible to measure the CO_2 directly several indirect methods for alveolar CO_2 determination in polio patients are presented (43, 136).

Most of the physiological interest in mechanical resuscitators has centered on cardiovascular problems. The comparative merits of a positive-negative pressure cycle and the positive pressure cycle only are still not settled. According to Maloney & Handford (113) animals with competent circulatory and respiratory systems tolerate either type of cycling without change in cardiac output. However, after embarrassment of the circulatory system positive-negative machines are distinctly superior in maintaining an adequate cardiac output and blood pressure. By direct measurements of the superior vena cava flow Brecher (26) has shown that with positive-negative pressure cycling the venous return was larger than with positive pressure cycling only. Price, Conner & Dripps (145) compared various resuscitators in 34 anesthetized patients. Blood pressure decreased in all proportionally to the mean positive mask pressure. This also applied to positive-negative machines where the mean pressure is positive.

Continuous positive or negative pressure breathing.—Here again the interest is primarily concerned with hemodynamic problems. Bjurstedt (21) described the vascular readjustments with positive pressure application before and after vagotomy. Recovery of the systemic pressure was never complete after vagotomy. He postulates that certain vagal reflexes normally prevent pooling of peripheral blood during pressure breathing by increasing the tone of the expiratory muscles of the abdomen. Support for this concept has recently come from the studies of Taugner *et al.* (177). For maintenance of man in the outer fringes of our atmosphere the lung has to be pressurized up to 150 mm. Hg., while counter pressure is provided by capstans. The cardiac output under such conditions is reduced to the same level as with 35 mm. Hg applied to the unprotected chest (30). Gauer and others had previously shown that oliguria was associated with continuous positive pressure breathing. With negative pressures dogs (66) and man (164) show a diuresis. On the basis of such findings an interesting hypothesis has been formulated, namely that stretch receptors in the vessels of the chest represent sensing mechanisms linking the hemostatic events with urine secretion for the control of plasma volume. With negative pulmonary pressure the distended blood vessels of the thorax would presumably signal a general hypervolemia.

Pulmonary Circulation

While the lesser circulation has in the past often been treated as an incidental or separate phenomenon in respiratory physiology our present day concept of gas exchange make it absolutely mandatory to include it on a par with the alveolar ventilation. In fact it is this realization that has in part prompted the great current interest in this particular field. It seems quite

appropriate, therefore, to mention first the changes in the pulmonary circulation observed at birth with the very first breath of air. The technically remarkable experiments of Dawes and associates (46) show in near term fetuses of the sheep that with the first few breaths of air, N_2, or O_2 (by positive pressure) there is an immediate increase in the pulmonary blood flow and a drop in the pulmonary arterial pressure. The resistance to ventilation is also decreased rapidly within the first 10 min. After tying the cord and initiation of ventilation the ductus arteriosis did not close for at least 1½ hr. and blood was observed to flow backwards from the aorta into the pulmonary aorta.

Pulmonary vascular resistance.—Whether or not the pulmonary vessels can independently control their vascular resistance is still a controversial issue. This apparently simple problem requires accurate determinations of the bloodflow as well as the pressure drop across the circuit, yet the current methods for obtaining these parameters have been criticized. Both Nahas *et al.* (129) and Leusen & Demeester (98) have shown that with low O_2 breathing in the dog the dye dilution method gives larger values for cardiac output than the conventional Fick method. When air is breathed, such differences disappear. The criticism directed against measuring pulmonary venous pressure in man by the "wedge" method has been discussed by Wiggers (189). At least five papers in support of this method have appeared since but are not reviewed.

With such criticism in mind we may now turn to the reported changes in the pulmonary resistance. A literature survey of the normal values of right heart and pulmonary pressure in man has been collected (58) and a good correlation has been obtained between the PAP^2 and the calculated resistance (59). During exercise PAP rose roughly proportional to cardiac output (18) suggesting no change in resistance. Acute atelectasis (1 hr.) of one lung in man does not alter its flow appreciably (19), however, in the chronically collapsed lung the flow is very much reduced in man (19) and the dog (154). With the aid of bronchospirometry an increased local vascular resistance in the low O_2 breathing lung has been reported by Heemstra (77) and Rahn & Bahnson (147) for the rabbit and dog, respectively. In both animals this response occurs rapidly, shifting the circulating blood to the high O_2 lung. In dogs where one lung was artificially perfused by its own arterial blood the resistance promptly increased when this lung was ventilated with a low O_2 mixture (75, 82). In the intact, anesthetized dog increased resistance has also been reported (82, 99) with low O_2 while in the unanesthetized dog Nahas *et al.* (129) indicate no change when they employ the dye dilution method for estimating the pulmonary flow. In patients with mitral stenosis pure O_2 inhalation reduced the vascular resistance in 10 out of 13 patients and suggested that part of the pulmonary resistance is normally attributable to local hypoxia (118). What appears to be a chronically increased resistance can be found in dogs acclimatized for several weeks to altitude. This is associated with a hematocrit rise to 75 per cent, but the periph-

eral circulation is unaffected (14). A 5 to 8 hr. exposure to chloralose-morphine anesthesia in dogs breathing room air produces a gradually increased resistance (100). Of considerable interest are the experiments of Kaunitz & Andersen (88) who performed a complete parasympathectomy of the lung in a two stage operation separated by four weeks. After complete recovery the pulmonary artery and right ventricular pressure averaged only 54 per cent of the preoperative value in 9 dogs out of 10. If one assumes that the cardiac output was not reduced to one-half in these chronically operated animals we may have here a permanent change in the vascular resistance after parasympathectomy. With complete sympathectomy of the lung Nahas and associates (130) were unable to demonstrate any pulmonary resistance change upon exposure to 8 per cent O_2 in the nonnarcotized dog. Bjurstedt & Hesser (22) discuss the resistance changes during the respiratory cycle. They believe that an increasing lung volume is accompanied by a rise in intramural pressure which tends to resist the increased flow during the inspiratory phase thus accounting in part for the increase in the effective PAP during inspiration. Rodbard (153) has provided a thought-provoking review concerning the possible role of bronchomotor tone in the regulation of pulmonary artery pressure and resistance.

In a series of ingenious experiments Sjöstrand (167) has been able to measure the redistribution of trapped blood released suddenly from the legs. Of the 600 cc. which are released 78 per cent is absorbed in the thorax and of this amount 75 per cent goes to the pulmonary vessels, the remainder to the heart.

Pulmonary artery obstruction.—Hackel *et al.* (73) have studied in dogs the pulmonary arterial hypertension induced by a suspension of lycopodium spores. Pulmonary resistance and cardiac output increase, but the systemic and coronary circulation remain unaffected. The left lateral position is the most favorable one for surviving air embolizations (intravenous injection) because air bubbles are probably trapped in one lung allowing free circulation in the other one (139). Another method of treatment consists of pressurizing the whole animal to 7 atm. (111). Air introduced on the right side is occasionally found in the left heart, and Hertz & Hertz (79) have devised equations for predicting the pressures necessary to drive air emboli through the pulmonary capillaries. Methods for the acute occlusion of the pulmonary artery as well as the bronchus or both have been described by Flores *et al.* (57), while Lategola & Rahn (96) have devised a "self-guiding" catheter which can be inserted into a dog's pulmonary artery without use of a fluoroscope for occlusion of arteries as well as pressure recording. Nordenström (134) has given a detailed account of the roentgenological changes of the pulmonary circulation when one artery is suddenly occluded.

Arterial-venous shunts and bronchial circulation.—More evidence has been presented which indicates that in man and animals pulmonary shunts of considerable magnitude can be opened under proper circumstances. An excellent anatomical study of these shunts as well as bronchial-pulmonary

anastomoses has been given by Tobin (180) and Hayek (76), while Sirsi & Bucher (165) have demonstrated shunts in various animals by the injection of radioactive glass spheres with diameters of 25 to 30 μ. More evidence for extensive anastomoses between the bronchial circulation and the pulmonary as well as coronary circulation has been presented (23, 74, 108, 134).

Circulation time.—The lung-ear circulation time is slightly increased in the maximum inspiratory lung position (24). With the fluorodensograph the travel time for radio-opaque materials between the right and left ventricle is 4 sec. in normal subjects (131), while the tracking of radioactive iodine with scintillation counters gives values of 5.8 sec. (162). When cardiac output is nearly doubled in man the median circulation time decreases approximately 35 per cent (38). A similar reduction was obtained by doubling the blood flow through one lung upon acute occlusion of the left pulmonary artery in the dog (135).

General

Effects of so-called inert and other gases.—It is becoming increasingly evident that besides O_2 so-called inert and noble gases are able to exert deleterious actions, particularly on the central nervous system. Carpenter has shown (35) that N_2, A, SF_6, and N_2O are all able to narcotize the central nervous system of mice, each gas having its own pressure threshold. Nitrogen narcosis can be used to protect against hyperoxic convulsions (36). As has recently been shown, xenon will anesthetize man at less than 1 atm., and the rate of radioactive xenon uptake in various tissues has been determined (143). Levy & Featherstone (104) have found no effect of this gas (0.8 atm.) on tissue respiration. On the other hand, South & Cook (169) report that tissue slices exposed to xenon show an increased O_2 uptake and depressed glycolysis. Martin & Ferguson (117) made the interesting observation that the radon output of individuals with residual radium deposits varies with posture. Since the radon release at the tissue site is presumably constant the lowered pulmonary excretion of this gas in the erect posture would suggest a vasoconstriction in the peripheral vessels including the bone where most of the radium is fixed. Of interest is the inert, synthetic gas, sulfur hexafluoride, of which the relative rate of diffusion in the tissues seems to be lower than that for any other known gas. When this gas is injected into the peritoneum the N_2 of the surrounding tissues diffuses faster into this cavity than the SF_6 can leave. The consequence of these diffusion differences results in a doubling of the peritoneal gas volume before it is slowly resorbed (179). It is probably the first gas known which will sustain a pneumothorax or pneumoperitoneum volume longer than air or nitrogen. Stockinger (170) has reviewed the literature concerning ozone toxicity. Its primary target is the lung, producing pulmonary edema and hemorrhage. It thus resembles, superficially at least, O_2 poisoning. The effects produced by high pressures of O_2, including its relation to retrolental fibroplasia (1, 141), are described by various workers (67, 68, 168).

Standards for children.—Maximum breathing capacity and vital capacity standards for female children (5 to 15 years) are given by Ferris & Smith (51) and follow previously published standards for male children. Arterial blood gas composition in normal children has been given by Cassels & Morse (37). The quantitative variations in the respiration of new born infants (81) and four successive stages of breathing patterns after birth (126) have been described.

Techniques.—For various types and modifications of respiration recording apparatus the reader is referred to the excellent book by Fleisch (55, 56). Perkins (142) has described a light weight, inexpensive vinyl plastic Douglas bag and Ganslen & Van Huss (65) a very light (700 gm.) apparatus for the collection of gases during exercise in the field. Boothby *et al.* (25) and Lundin (110) discuss their new modifications of the N_2 analyzer as well as the interpretation of the N_2 elimination curves. Clark *et al.* (41) have described a construction of a small platinum cellophane covered cathode for measurements of O_2 in whole blood. Lazarow (97) has published a new method for blood gas analysis on 20 microliters of blood. An improved technique for the Van Slyke blood O_2 analysis has been described (47). Verzar *et al.* (184) have measured the water vapor saturation in various parts of the respiratory tract. Mechanical heart-lung machines have been described (123) as well as a new oxygenator pump for use in total bypass of the heart and lung (78).

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THE DIGESTIVE SYSTEM[1]

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Introduction

In reviewing the literature for the last year pertinent to the Physiology of the Digestive System, it should be pointed out that no attempt will be made to include all the clinical papers that have appeared in the medical literature. Only such references will be included that appear to have some physiological significance.

However, before entering into this assignment, it would seem appropriate that we remind ourselves that the year 1953 marks the centennial of the death of William Beaumont, the "Father of American Physiology." Palmer (1) in a timely editorial refers to the high lights of his accomplishments as an experimenter and writer and quotes Harvey Cushing's words that Beaumont's famous monograph is "the most notable and original classic of American medicine."

It also seems appropriate to commend the Michigan State Medical Society (2) which has recently restored the old retail store of the American Fur Company of Mackinac Island, Michigan. This is to be preserved by the State Park Commission as a medical shrine and one of the chief centers of Beaumont interest in this country. It goes without saying that the group interested in the physiology and medicine of the gastrointestinal tract are very grateful to the medical men of Michigan for undertaking this lasting memorial to one of America's great men of physiology.

Mouth

Sensory and motor activity.—In reviewing this field one is impressed with the trend toward the study of physiological behavior of microscopic structures of the tongue and mouth parts. A few major contributions will be mentioned. Gairns (3) in his studies on early post mortem material finds that the surface of the tongue of the adult human shows very few taste buds, apart from those on the circumvallate papillae, but a very extensive network of myelinated nerve fibers branching out in the superficial dermis to form thinner nonmyelinated branches which penetrate into the epithelium to form free intraepithelial endings. He also noted Meissner and Krause type nerve endings as well as a profuse, fine, subepithelial plexus of bearded fibers which appear to be of sympathetic origin. In a later study Gairns (4) examined the hard palate and found, along with free sensory nerve endings in the subepithelial and epidermal layers, many forms of organized endings in the dermal papillae. In particular he reported the presence of a nerve ending that was very characteristic of this region which he called "ultra-terminal"

[1] The survey of literature pertaining to this review was completed in June, 1954.

fibers, which pass into epidermis and then extend in a relatively straight course to the outermost layers of the epithelium. No such "ultra-terminal" fibers were found in the soft palate or uvula. Likewise, Cooper (5) made histological sections of tongues of different aged humans, as well as of monkeys, new-born kittens, and lambs, and noted that the muscle spindles associated with the proprioceptor sense organs of the human and monkey (but not of the cat and lamb) are associated primarily with the intrinsic muscles. Landgren *et al.* (6) recorded action potentials from the lingual branch of the glossopharyngeal nerve of *Rana esculenta* with stimuli of both water and hypertonic NaCl solutions on the taste buds. They found that appropriate doses of acetylcholine would increase the sensitivity to the two tests.

That the normal physiological state of the membranes of the mouth is dependent upon a certain nutritional state is demonstrated by the work of Baume & Frandsen (7). They found by using a phase contrast microscopy technique that young male rats (14 days of age) which survived an 86-day experiment on a vitamin A-deficient diet showed marked changes in the biostructures of the oral epithelium; namely, an aplasia of the basement membrane, a precocious disintegration of the tonofibriles in the stratum spinosum and a parakeratosis of the surface layer. Likewise Engel (8) demonstrates that in certain pathological states the connective tissue of the gingiva contain appreciably greater amounts of water soluble mucoproteins and carbohydrate then normal tissue. He attributes the change to an enzymatic depolymerization or to some altered synthesis of the connective tissue ground substance.

A few papers concerning the relation of minerals to dental caries are of physiological significance. Both Besic (9) and Bernick *et al.* (10) demonstrated typical macroscopic characteristics of true caries of the dental enamel. Besic showed that caries can be duplicated *in vitro* by exposing teeth to solutions of lactic, acetic, hydrochloric, and carbonic acid. It was interesting to note than when high concentrations of calcium and phosphorus ions were added these acids caused no change in the enamel. The evaluation of various fluoride treatments of caries is also reported (11, 12).

Of special interest to the aviation physiologist is the work of White, Roberts & Merideth (13), who report a relationship between dental overbite and aerotitis media. From an examination of 147 commercial pilots and stewardesses they learned that there is a relationship between the grade of incisal overclosure and the habitual use of the valsalva maneuver in flight, and the occurrence of aerotitis media. They discuss how the overbite might produce a hypoventilation of the middle ear as well as cause a derangement of the soft tissues of the eustachian canal.

Salivary secretion.—Emmelin and his associates have already made remarkable contributions to our knowledge of the intricate mechanism of salivary secretion, unexcelled since the days of Claude Bernard. His more recent experiments (14) yield equally classic observations on the spontaneous activity of the cells of the sublingual gland of the cat. He observes that in the anesthetized cat there is a continuous slow flow of a very thick saliva

which cannot be collected from either the submaxillary or parotid glands. This flow can be accelerated by stimulation of the chorda tympani or sympathetic trunk in the neck or by injections of acetylcholine, epinephrine, or pilocarpine. There is no way of stopping the basal level of flow by denervation (acute or chronic) or by the administration of atropine or other depressant drugs. The secretion continues also in the isolated profused preparation. The only way it can be stopped is by the addition of sodium cyanide to the perfusion fluid.

Emmelin & Stromblad (15) also report on the effect of section of the chorda-lingual nerve in eight nonanesthetized dogs supplied with chronic fistulae of the submaxillary ducts. The operation temporarily abolishes all reflex secretion, but after a period of time, varying up to several weeks, a slight secretion can be observed even when no food is supplied. The secretion is evidently a conditioned reflex; since it is obtained even after removal of the superior cervical ganglion, it is concluded that some secretory nerve fibers reach the gland by an anatomically unknown path. This secretion should be distinguished from the "paralytic secretion" originally described by Claude Bernard. Emmelin & Henriksson (16) also report on the depressor activities of saliva collected from the submaxillary gland of the cat after the injection of epinephrine. The activity was found to diminish gradually after section of the chorda tympani, to reach a level of 10 to 75 times below the original. A similar change occurred during prolonged treatment of a cat with a parasympathetic drug. The mechanism of action of this effect in the salivary gland is surely worthy of further study. Much credit should also be given to Richins & Kuntz (17) for their study on the role of sympathetic nerves in the regulation of salivary secretion in the cat. It is their conclusion that the parasympathetic nerves make direct connection with the secretory cells of both the parotid and the submandibular glands, but that the sympathetic nerves supplying these glands are distributed predominantly, perhaps exclusively, to the blood vessels of the gland. They support this concept by the fact that occlusion of the blood supply to these glands always prevents secretion caused by sympathetic stimulation but has no immediate effect on parasympathetic secretion. It is further supported by experiments in which adrenergic sympathetic stimulation of the submandibular gland causes copious secretion. Cholinergic parasympathetic stimulation also elicits an abundant secretion from the gland, but only after the adrenergic nerve components have been depressed. It is information of this sort that takes the mechanism of salivary secretion out of the realm of the theoretical into the confines of the factual.

Lundberg (18) and Burstone (19) also report on the nature of salivary secretion.

Properties of saliva.—Of great importance are the factors that govern acid-base balance of saliva. A significant piece of work has been done by Takaoka (20). He points out that the concentrations of extracellular salts (Na, Ca, Cl, and HCO_3) in natural saliva are lower than those in blood serum and increase when the excretion of saliva is stimulated. On the other hand

the concentrations of intracelluiar salts (K, P, and NH_4) are higher in natural saliva than in serum and are decreased by quickened excretion. Often during excessive production of saliva the concentration of bicarbonate in the saliva surpasses the bicarbonate concentration of the blood. Thus the concentration of bicarbonate in saliva cannot come entirely from the blood, and it is suggested that bicarbonate may be formed in the cells from CO_2 and the H ion of H_2CO_3 exchanged with the Na ion in tissue fluids. This is further supported by Dreizen *et al.* (21) who suggest that the greater buffering power of stimulated saliva, as contrasted with resting saliva in the same person, is attributable to the increased secretion of sodium and bicarbonate. Another important contribution is the actual in situ measurement of the rate of human salivary buffering in response to acid stimulation by Oster *et al.* (22). His is a unique approach and one of considerable physiological significance. The method consists in placing a glass H ion electrode under the tongue with the calomel electrode kept in contact with the skin of the hand so that any change in pH could be recorded whenever desired. They recorded normal or resting pH; then after removing the glass electrode from the mouth, the subject drank approximately 3 oz. of one of 11 different beverages, upon which the electrode was replaced and pH reading taken every 20 sec. until the pH leveled off to the normal resting levels or a more alkaline level. This took from 2 to 5 min. The shift toward alkalinity was achieved by the concentration of buffer in the saliva and the rate of salivary flow. The actual results show that the normal pH in 195 subjects was 6.07 with a range of 5.73 to 6.15. When drinking carbonated beverages which gave an average of pH 3, the buffering response of saliva was very rapid. Of all the different beverages tested 96 per cent produced a positive buffering effect in less than two minutes.

That saliva possesses different properties throughout the day is demonstrated by Bonicke and his associates (23), who showed that night saliva collected immediately upon waking has a very high antibacterial activity compared with saliva collected during the day. The difference is attributable to a concentration factor, since the slow flow of saliva during sleep allows the active agent to accumulate. Takaoka and his associates (24) report that there is a seasonal variation of secretory rate and acid-base balance in saliva. He says that the secretory activity produced by a dilute acid stimulation increases in the spring, attaining a maximum in May, and reaching its lowest rate in the late autumn and winter. The bicarbonate concentration increases with an increased secretory rate of flow. Hoffmeister & Albrecht (25) show that after pilocarpine injection the Na concentration of saliva increases and the K concentration decreases and that this response is greater in patients with adrenal insufficiency and smaller with patients with hyperadrenocorticism. Desoxycorticosterone decreases salivary secretion of Na and increases the K secretion.

Many isolated reports on salivary composition have appeared. It is hoped these will contribute eventually to a comprehensive analysis of the secretory mechanisms taking place in the salivary cells. For those interested the fol-

lowing are listed: Polarographic studies of saliva (26); uricolytic ferments in human saliva (27); presence of leucocytes in saliva (28); citrate content in saliva (29); folic acid and vitamin B_6 in saliva (30); importance of O_2 in the production of acid in glucose saliva mixtures (31); alkaline reserve of saliva as related to caries (32); carbonic anhydrase concentrations of the different salivary glands (33).

Esophagus

No major observations have appeared recently relative to swallowing, with the exception of a few important papers on the third, or esophogeal, phase of swallowing. However, there appeared an interesting review pertaining to the history of the swallowing mechanism (34). In it was a statement by Hippocrates generally accepted until 1747 which may afford some bit of comfort as to how far our knowledge of the digestive system has advanced in the last 200 years:

> When liquid is swallowed, a portion goes to the lung and from there is filtered into the Pericardial sac, where it lubricates and cools the feverish heart. The rest of the liquid is exhaled as vapor.

Likewise it has taken more than 20 years to apply to the esophagus the concept of negative pressures in relation to the act of swallowing as described by Barclay.

Concerning the motor mechanism of the act of swallowing involving the esophagus, and in particular the distal portion, Sanchez and his associates (35) obtained recordings of intra-esophageal pressures after dry liquid or barium substances were swallowed to show the general characteristics of the swallowing pressure patterns. They intubated the esophagus with two soft No. 10 intravenous catheters so attached that their distal tips were 8 cm. apart. The open tipped catheters were filled with water connected to electromanometers. The observations made of the upper $\frac{7}{8}$ of the esophagus coincide fairly closely with those previously obtained by Butin *et al.* (35a) in 1952. The author described these movements very lucidly but they will not be discussed here. The physiology of the terminal 2 to 5 cm. of the esophagus, where the swallowing complexes are decidedly different, will be referred to briefly. This area of the esophagus is often referred to as the vestibule and corresponds in most cases to the upper margin of the diaphragmatic shadow. It can be located by letting the open-tipped catheter go into the stomach and then pulling it back until the inspiration first produces a negative deflection in the pressure recording. The results show that in half the cases studied there is no change in intraluminal pressure after swallowing. In the other half, the recording shows a type of "vestibulae" swallowing complex which differs markedly from the upper $\frac{7}{8}$ of the esophagus in that it shows (*a*) absence of the first positive wave and pressure plateau which is always present in the upper esophagus following the swallowing of liquids, (*b*) a maximum pressure of only 5 to 15 mm. of Hg as against 40 to 100 mm. of Hg in the upper esophagus, and (*c*) a very gradual increase and decrease in

intraluminal pressure extending over a period of 20 to 40 sec. which is not propagated into the vestibular area. It is suggested that the distal portion of the esophagus possesses an independent motor function and does not respond to swallowing in the same manner as the rest of the esophagus. The authors think that this may explain why opaque fluids often may remain for some time in the pouch-like dilatation of the esophagus immediately above the diaphragm and why it is often difficult to distinguish between it and small diaphragmatic hernias.

Hwang (36) studying the mechanism of functional recovery of the cervical portion of the esophagus, reports that bilateral section of the pharyngoesophageal nerve in the dog and cat causes a paralysis of the cervical portion of the esophagus so that symptoms of dysphagia and regurgitation of food during a meal are present. This condition is transitory, and recovery results in three to five weeks. The mechanism for recovery is said to be the taking over by the recurrent laryngeal nerve. If the dogs are now bilaterally vagotomized a second paralysis of the esophagus occurs. Stimulation of the peripheral vagus or the recurrent laryngeal nerve causes a contraction of the cervical portion of the esophagus. That a double nerve supply to the esophagus of the dog may exist has led Hwang & Grossman (37) to investigate the innervation of the cervical portion of the human esophagus in fresh cadaver specimens. There is no direct evidence for this pattern of innervation of the upper esophagus, and the need for further study is suggested. Hightower, Olsen & Moersch (38), in making a comparison of the effects of methacholine (Mecholyl) on esophageal intraluminal pressures in normal persons and patients with cardiospasm, report that patients with cardiospasm are very sensitive to methacholine administered intramuscularly in 6 to 10 mg. doses; this was not observed in the control group of normal persons. In some patients after operations on the cardia for cardiospasms there often occurs an incompetent cardia. According to Schmidt (39) this allows gastric contents to regurgitate into the lower part of the esophagus and produce esophagitis and sometimes ulceration at the esophago-gastric junction.

Stomach

Sensory and motor activity.—The outstanding contributions to our knowledge of the stomach during the past year deal with the nervous system in relation to the stomach. This approach will surely lead to a fuller understanding of the different phases of stomach physiology.

Much credit should be given to Eliasson (40) who presents interesting observations on the activation of gastric motility by stimulation of the brain stem and associated structures in cats. As many as 15 different neurological areas or centers are listed by him as being responsible for causing an increase in motility. On the other hand eight areas are identified as causing inhibition of gastric motility. The excitation effects elicited from the thalamus had lower frequency optimum and longer duration optimum than the inhibitory stimulatory effects. The efferent pathways were in both the splanchnic and vagus nerves. All excitatory effects were abolished by atropine, as were the

inhibitory effects conducted through the vagal nerves. It is expected that this type of work will stimulate further investigation.

Next we commend the work of Chinn & Wang (41) who further elucidate the central emetic mechanisms with their studies on irradiation. They briefly review the recent concept that the central emetic mechanism consists of two emotionally close, but functionally distinct, areas: a chemoreceptive trigger zone, and the actual vomiting center. The trigger zone prevents vomiting from "central" acting drugs (apomorphine, morphine, etc.) but does not affect vomiting after orally administered $CuSO_4$. The observation that a non-chemical motion sickness stimulus in dogs can be prevented by previous destruction of the trigger zone prompted the authors to make a surgical ablation of the trigger zone to record its effects in preventing emesis in dogs after irradiation. They fed dogs commercial dog food and 30 min. later irradiated them with 300 to 800 r and observed the frequency of vomiting within from 4 to 6 hr. Then six to eight months after removal of the trigger zone they repeated the experiment. The results show that 12 dogs exposed to 800 r vomited within 2 hr. after completion of the irradiation, but no dogs subjected to bilateral destruction of the emetic chemoreceptor or "trigger" zone vomited after 800 r exposure.

Likewise the observations of Littman *et al.* (42) who studied the effects of nearly uniform exposures of lethal doses of radium, strontium, and ruthenium-rhodium on the mucosa and the nature of their action are especially noteworthy. They mounted radioactive isotopes in balloons which were then anchored in the stomach. When the balloon was inflated, the radioactive material was in the center of the balloon. After lethal doses were given the following observations were made. Appetite: dogs began to eat less after the third week. Vomiting: very persistent after the third week. Dehydration: weight loss from 36 to 52 per cent. If gastrectomy was performed after lethal exposure death was prevented. These observations also demonstrate the need of a better understanding of the nerve pathways involved in stomach activity. Also of value is a symposium by Hollinshead, Smith & Kolb (43) on the anatomic pathways of pain originating in the upper part of the abdomen. They conclude that visceral pain is transmitted largely by the splanchnic nerves. They also discuss the various patterns of pain associated with the stomach, duodenum, pancreas, and emotional disturbances.

Concerning the stimuli of pain in the stomach area Stunkard & Wolff (44) worked on hunger contractions in man, and reported that intravenous injections of 50 cc. of 50 per cent glucose promptly abolished gastric contractions of hunger. When simultaneous determinations of venous and arterial blood glucose under these conditions were made it revealed an arteriovenous glucose difference of the order of 20 mg. per cent and when this difference returned to zero there was a return of both gastric hunger contractions and the sensation of hunger. In cases of hypothyroidism Mendelson & Curtis (45) report a relationship between gastric motility and abdominal pain, which decrease after treatment with desiccated thyroid. According to Kinsella (46) the pain associated with chronic gastric ulcers is caused by a

deep and punched out type with a floor of small area and rolled edges full of neural end bulbs. On the other hand, those ulcers which are superficial and shallow and have a wide floor are more often painless. The author suggests that the cause of the pain is not from the floor of the ulcer but from the edges, and that acid pepsin cannot be the primary cause. Gray *et al.* (47) discuss in some detail the significance of hormonal factors in the pathogenesis of peptic ulcers. Their studies suggest that chronic emotional and physical stress stimulate the stomach to secrete increased acid and pepsin by way of a hormonal mechanism involving the hypothalamic pituitary-adrenal-gastric axis independent of the vagus nerve or the gastric antrum. The authors accept the importance of the vagus as a factor in the production of ulcers but emphasize the importance of the hormonal mechanism as well.

Still another approach to studying gastric motility in man which has exciting possibilities is the use of a new type of electrode for measuring potential differences of the human stomach reported by Ingram & Richards (48). In their experiments one electrode is placed on the outer aspect of the right arm and the other is passed through the nose into the stomach. The observed potential differences are correlated with the regular 20 sec. cycle as being related to normal gastric contractions. Evidence is given to show a difference between normal and diseased stomachs.

With this technique the knowledge of drug action in the human could be advanced considerably. No attempt will be made here to discuss the effects of drugs and vitamins on gastric motility or emptying time of the stomach, although several interesting papers have appeared (49 to 53).

From the extensive work of Quigley & Loucks (54), who used the inductographic technique to study tone of the pyloric sphincter in trained dogs, we have the following statements. The pyloric sphincter tone remains remarkably constant from day to day and month to month. Noxious stimuli, such as slapping or sudden loud noises, usually cause a 5 to 10 per cent increase in tone for 20 to 60 sec. Tone is also higher in fasting than in well fed animals; during the first and second hour-interval following a meal the tone decreased 1 to 15 per cent below the fasting level. Bilateral section of the vagi had little effect on the tone of the sphincter. Atropine in small doses failed to alter sphincter tone, whereas large doses decreased tone 5 to 10 per cent for 60 to 90 min. Epinephrine in small doses also was without effect but large doses decreased tone for only 1 to 5 min. Pilocarpine increased tone 1 to 10 per cent for 10 to 30 min. They also report (55) that 7 per cent $NaHCO_3$ solutions placed in the stomachs of normal, fasting unanesthetized, trained dogs, caused a marked increase in tone of the pyloric sphincter as well as in amplitude of contractions. They conclude by pointing out that these observations are contrary to previous claims, which state that $NaHCO_3$ "props open" the pyloric sphincter.

Gastric secretion.—In view of the extensive literature available on gastric secretions and allied subjects, the material can best be presented under a number of subheadings with a few observations on each.

a. Cellular secretion: Under this topic we refer to the literature that per-

tains to the nature of the active secretion by the parietal and peptic cells. First we have the work of Rehm, Schlesinger & Dennis (56) who tested a theory of HCl formation that the chloride ions are secreted by the surface epithelial cells and the hydrogen ions by the parietal cells. They argued that hypertonic neutral salts in contact with the resting gastric mucosa should produce considerable water transport and hydrogen and chloride ion output. However, it was found that actually only a very small net water transport occurred as compared to the average water output during normal secretion, and it was concluded that the theory was untenable. On the basis of these findings and those of other workers they suggest a new hypothesis: that the hydrogen ions are secreted by the surface epithelial cells and the chloride ions by the parietal cells. Davenport & Chavre (57) in recording the acid secretion and O_2 consumption by the mouse stomach *in vitro* find that the properties of the mammalian gastric acid secretory process are similar to those of the frog. From the different recordings made they report that glycolysis contributes markedly to acid secretion and dinitrophenol inhibits it without affecting O_2 consumption. That the level of gastric HCl is related to blood chloride concentration is reported by Lahiri (58) who noted that in people with low chloride levels, resulting from cholera, anemias with associated low blood chloride levels, or low salt diets, there is also deficiency in acid gastric secretions. He also reported that most people with hypersecretion gave subnormal blood and urinary chlorides because of excessive drainage of the chloride through the gastric juice.

Relative to pepsin-secreting cells, Villarreal (59) used the isolated stomach of the mouse. His results show the presence of a basal rate of pepsin secretion, and that .1 mg. per cent of carbaminoylcholine increases the rate of secretion by 300 per cent. Atropine inhibits the additional secretion but not the basal rate. Histamine slightly stimulates pepsin secretion. With the stomach supplied with amino acid mixtures there was no additional pepsin synthesis. Zwarenstein (60) by filling the isolated frog stomach with an acid solution and suspending it in Ringer solution, noted that a perforation of the stomach wall occurred near the cardiac end, probably attributable to the action of pepsin on the gastric mucosa membrane. The optimum pH of the inserted solution to give the fastest action of pepsin on the stomach wall varied directly with the temperature.

b. Nervous and chemical control: Under this topic it will be evident that there is a relationship between these two mechanisms of control of gastric secretion. For example, Burstall & Schofield (61) report that dogs with Heidenhain pouches respond to central vagus or brain stimulation with a small but definite effect on secretion. They suggest that either a few vagal fibers could reach the pouch via blood vessels, or that gastrin is released from the main stomach on vagal stimulation and in turn affects the pouch via the humoral pathway. Removal of the pyloric end of the stomach, the main source of gastrin, shows that the latter mechanism is more tenable. Evans *et al.* (62) using both Pavlov and Heidenhain denervated fundic pouch dogs, recorded the daily gastric juice output for approximately 30 days. Then by

cutting the vagi to the main stomach they got a marked increase in secretion in both the Pavlov and Heidenhain pouch dogs. If the antrum was removed in the denervated stomachs the secretion rates in the Heidenhain pouches were markedly reduced. If the antrum was retained and the fundus of the main stomach removed, the Heidenhain pouch increased in rate of secretion. These results support the view that the vagus is related to the gastric phase of secretion. As to the manner in which vagotomy affects the composition of the secretions from Heidenhain pouches we refer to the work of Ferguson (63) and Linde (64) who find that when the vagus stimulates the denervated Heidenhain pouch to secrete via the antrum the secretion of pepsin is little affected. The importance of the gastric antrum in the control of gastric secretion is shown in a report by Dragstedt, an eminent investigator in this field (65). When he removes the antrum of the stomach from dogs provided with a Heidenhain pouch, the secretions of gastric juice from the pouch are negligible. Likewise, a similar reduction occurs when the antrum is transplanted into the abdominal wall where it does not come in contact with food. If, on the other hand, food is introduced into such an isolated antrum there occurs a stimulation of gastric secretion from the Heidenhain pouch. If acid is placed in the antrum pouch an inhibition of gastric secretion from the Heidenhain pouch occurs.

c. Effects of drugs: It is not within the scope of this review to dwell on the effects of drugs; therefore only a few publications of major physiological significance will be referred to. An important contribution is made by Thompson & Vane (66) who perfused the isolated stomach of cats with heparinized blood through the coeliac axis. The stroke and rate of the perfusion pump could be varied at will. A glass cannula was tied into the pyloric end of the stomach for collection purposes and the oesophagus was ligated in the neck. To stimulate gastric secretion they used histamine, which also increased the blood flow to the stomach. The gastric secretion rate was measured at 10 min. intervals. The total perfusion lasted 2 to 4 hr. It took 30 to 40 min. to register an effect in secretion rate after changing the blood flow. The experiments showed that, with the infusion rate of histamine kept constant, the increase in blood flow always caused a rise in secretion rate. This factor was more effectual than changes in perfusion pressure. The results show that the concentration of histamine in the blood is not the only important factor in causing gastric secretion. The rate of blood flow is also important. The effect of epinephrine, which causes constriction of blood vessels, decreased the gastric rate of secretion. Likewise stimulation of the left splanchnic nerve also caused a decrease in secretion. Using the same technique as that just reported, Born & Vane (67) showed that if histamine is in contact with the perfusion blood for about 1 min. before reaching the stomach the rate of secretion is greater than if the blood-histamine contact is shorter. This suggests that there is an indirect action of histamine on the mucosa cells.

Kay (68) reports some interesting observations on the standardization of the histamine test. He points out that in the usual histamine test the dose

has been determined arbitrarily and fails to take account of individual variations and susceptibilities. His test requires increased histamine until a constant and maximum rate of acid secretion is obtained, and giving antihistamine 30 min. before the histamine, which counteracts all side effects save gastric secretion. The test is made after 12 hr. fasting, and secretion is recorded for 45 min. after the last histamine injection. The maximum output is reached in 10 to 15 min. and persists for the next 30 to 35 min. The results show that in normal subjects the average basal output is 70 mg. with an average maximal output of 422 mg. With duodenal ulcers this is 265 mg. for basal and 837 mg. for maximal, while with gastric ulcers the average basal is 113 mg. and the maximum is 478 mg. The author regards gastric secretion of HCl as of an "all or none" nature, i.e., there is no secretion by parietal cells until an effective stimulus is applied and then they all secrete maximally. He also asserts that the routine test meal is futile and is effective only in determining the presence or absence of free HCl. The advantages of this test are that it imposes a uniform stimulus which exerts a full load on the acid secreting cells and that its results are duplicable.

The need of finding the proper depressant drug for gastric secretion with a minimum of side effects still demands the consideration of the physiologist as well as the clinician; a few recently reported should be noted. Schwartz and his associates (69) report that Probanthine, a new anticholinergic drug, diminishes the volume of gastric secretion and inhibits gastrointestinal motility with much smaller doses than methantheline (Banthine), and with fewer side reactions. For further information concerning drug action on gastric secretion, we refer the reader to (70 to 74).

d. Miscellaneous factors: Papayannopoulos *et al.* (75) studied nocturnal gastric secretions in normal persons and patients with ulcers. They observed that there is a continuous, spontaneous secretion of gastric juice during the night (10 p.m. to 7 a.m.). The volume of secretion and acid content of ulcer patients was 40 per cent greater than that of normal subjects. Both groups showed a tendency toward acid disappearance between 3 and 7 a.m. The concentration of acid in the summer months was very low compared with that in the winter months. Nesterova (76) observed that gastric and duodenal ulcer patients gave increases in gastric secretion in the hunger state over that of normal, which was reversed with prolonged medicinal sleep. This effect was noted more markedly if the patients had been on a predominantly carbohydrate diet. Fox *et al.* (77) report on the effects of intragastric irradiation on the gastric acidity in the dog. By placing cylinders containing radioactive isotopes in balloons and passing them into the stomach via the esophagus or gastric fistulae, the effects on gastric acid could be determined. The dosage ranged from ineffective to lethal. The therapeutic dosage was considered to be present when a significant reduction of gastric acidity occurred, lasting for two to eight months and with minimal or no side effects.

e. Measurement of gastric secretion: In a recent editorial review, Segal (78) discusses the importance and nature of the action and development of the tubeless techniques for measuring gastric secretion, which he first intro-

duced in 1950. He states that any practical technique which offers pertinent information regarding gastric secretion without the disadvantages inherent in intubation should be welcomed both by physician and patient. He developed a combination of methylene blue, fluorescein, or azo dyes with various ion exchange resins. The principle is based on the fact that H cation desorbs the indicator ion, as quinine, from the insoluble compound, and that then the desorbed ion becomes available for absorption into the blood and is excreted into the urine. Thus the amount of desorbed indicator ion excreted in the urine within a predetermined time establishes the degree of acidity within the limits stated. The use of an insoluble salt such as quinine carbonate, which reacts stoichiometrically with dilute HCl solutions, has recently been reported by Segal & Miller (79) to be a good quininium cation that will serve well as a specific exogenous indicator ion. They suggest that relatively large doses of quinine carbonate may make it possible to differentiate between normal and high gastric HCl secretion without intubation. Conway & Meikle (80) report in achlorhydric patients they were able to collect only 20 μg. of quinine in the urine during a 2 hr. period after the subcutaneous injection of histamine and 2 gm. of the cation exchange resin preparation. Pollard *et al.* (81) report on an evaluation of the quininium cation exchange indicator "Diagnex" on 75 patients. The authors conclude that the test is very simple and extremely reliable for the detection of achlorhydria, but the use of the test as an aid in differential diagnosis of gastrointestinal lesions is limited.

It is rather amusing that the above described method used to determine the presence of acid secretions should be based on the discovery of Brücke in 1860, who observed that uropepsin can be correlated with gastric pepsinogen secretion, an observation that has been since confirmed by Bucher, Janowitz, and Hollander. Strangely enough, there is no relationship between urinary uropepsin excretion and gastric HCl as established by Anglesio & Forneron (82). Strehler (83) noted that caffeine, black tea, and smoking increased the uropepsinogen content even more than histamine. He also noted that hunger, nervous tension, and certain foods caused an increase of uropepsinogen in the urine, an observation which lends support to the fact that uropepsinogen is related to the nervous phase of gastric secretion.

Bolt *et al.* (84) found that feeding or injecting pepsin intravenously caused no increase in uropepsin. They also found that the oral administration of pepsinogen had no effect; but a marked increase in uropepsin excretion followed intravenous injection of pepsinogen. This suggests that uropepsinogen might be of value in diagnosing gastric gland function during different lesions. However, some of the difficulties present in performing the test and collecting accurate urine samples militate against the method as being ready for routine diagnostic procedure. Garst & Hilliard (85) have correlated the excretion of uropepsin with the activity of the adrenal cortex. They found that in young men there is at least a low correlation between 24 hr. uropepsin excretion levels and 17-ketosteroids, and consequently believe that the adrenal cortex may exert a controlling effect on uropepsin excretion. In older men they found the reverse correlation.

f. Mucosal protection and ulceration: The extensive work of Grant, Grossman & Ivy (86) on the histological changes in the gastric mucosa during digestion points to another interesting response of body tissue when physiologically stimulated. They observe that the histological appearance of the mucosa in the second to seventh hour of digestion of meat in dogs, cats, and kittens is markedly different from that of the fasted animal. During the digestive period the loss of gastric cells and changes in the mucosa are similar to the effects produced by mild irritants and the restoration of the mucosa takes place in the interdigestive period. It is suggested that the restoration of the mucosa to its fasting state involves movements of individual cells as well as transformation and synthesis of new cells. The authors point out that the maintenance of a normal mucosal pattern depends on a continuous and integrated functioning mechanism which controls loss and replacement of cells, that any interference with these mechanisms would lead to abnormal growth patterns.

Janowitz & Hollander (87), after collecting mucin from Heidenhain gastric pouches, studied various factors pertaining to its viscosity. They report that the initial high viscosity of mucin is lost upon incubation at 37°C., and that this process is speeded up by addition of cysteine and retarded by oxalate or citrate ions. It has a pH optimum of 6.0 to 6.5. The addition of trypsin, papain, and pectinase liquefies mucin, but salivary amylase, lysozyme, and soya bean trypsin inhibitor have no effect on the process of spontaneous liquefication. It is suggested that liquefication of the mucus layer in the stomach is constantly taking place, under the influence of a local mucolytic enzyme.

Haeger *et al.* (88) report on the effect of hypophysectomy or adrenalectomy on the gastrointestinal mucosa. They conclude that the maintenance of the structural integrity of the gastrointestinal mucosa is dependent on the pituitary gland and that hypophyseal control is, at least partly, mediated by the adrenal glands. Selye (89) presents an argument concerning the acquisition of tissue resistance to digestion by gastric juice. After making a "granuloma pouch" in the rat and then treating it with an irritant (croton oil) so that subcutaneous connective tissues are affected, he finds that the application of fresh gastric juice has no effect on the exposed tissue. If, however, a severe systemic stress is applied to the rat, such as a combination of fasting and neuromuscular exhaustion, the resistance of the irritated connective tissue to gastric juice is abolished. He concludes that no special protective substance of gastric origin need be invoked to explain the well known resistance of a gastric ulcer area to peptic digestion. Surely, further study of this cellular resistance mechanism would be valuable.

g. Composition and properties of gastric juice: Hiller & Bischof (90) by using paper electrophoresis and paper chromotography found five different protein components in gastric juice from normal persons, but in pathological juices there was an increase in fraction 5; in a number of cases of gastritis this was the only fraction found. There was no difference in amino acids between normal and pathologic patients.

Paper electrophoresis studies of mixtures of gastric juice and radioactive vitamin B_{12} by Schilling & Deiss (91) show that radioactive B_{12} is bound to a component of gastric juice which is different from the other major protein peaks observed. This reaction does not occur when mixtures of saline or blood serum are substituted for gastric juice. The results may be a clue to the further identification of the intrinsic factor of Castle.

Yamamoto & Chow (92) describe a quantitative method for determining the binding power of gastric juice for vitamin B_{12} by the use of resting cells of *Lactobacillus leichmanium*. They determined that samples of gastric juice obtained from pernicious anemia patients and aged individuals without achlorhydria had significantly lower binding power than control samples. Noer (93) reports on the ability of various areas of the gastric mucosa to bind vitamin B_{12}. He found that the pylorus mucosa is very effective, whereas the fundus and muscularis shows less or no effect.

h. Absorption from the stomach: In studying the effects of emulsifying agents on the digestion of fats in dogs with chronic stomach fistulas, it was noted by Zapolskaya (94) that when they were fed oxypolymerized oil added to margarine there was a definite increase in the amount of digestion of the fat present. Barkham & Tacantins (95) report on the effects of gastric juice on the ability to digest blood clots, and find that the lytic activity of normal human gastric juice is a function of the concentration and pH of the juice. The movement of potassium, sodium chloride, and water across the rumen epithelium of sheep is reported by Parthasarathy & Phillipson (96). They measured the net change that occurs in the solution placed in the rumen and compared this change with the venous-arterial difference between blood leaving the rumen and carotid blood. The results show that Na and K were absorbed from the rumen when the concentration exceeded that in the blood. Chloride was absorbed from the rumen against a concentration gradient. The presence of .002 M mercuric chloride inhibited the absorption of chloride, but did not affect the absorption of K and Na. The absorption of water from solutions of .165 M strength or less also occurred.

Also worthy of mention are the measurements of the absorption of water by the normal human stomach by Code *et al.* (97). Their method consisted in using 41 to 51 gm. of deuterium oxide which was swallowed and washed in with 50 cc. of water. In some cases barium sulphate was added for fluoroscopic recording. The measurement of absorption was made by collecting venous and radial artery blood samples at 2 to 10 min. intervals and then determining the concentration of heavy water in the plasma and urine by mass spectrometric analysis. The authors report that the rate of appearance of deuterium in the blood and its ingestion in the stomach is constant and can be followed accurately, also that most of the material remains in the stomach during all or most of the first hour of observation.

Gall Bladder and Bile

Bile secretion.—By perfecting an isolated liver preparation Brauer and his associates (98) were able to produce a steady bile flow for considerable

periods of time. The results showed that bile flow is a function of blood flow through the liver, and that the rate of bile flow can vary over wide ranges without affecting the maximal bile secretion pressures. It was also shown that bile production ceases when the temperature of the perfusion medium is down to 25°C. and reaches a maximum between 38° and 40°C. The authors conclude that bile formation involves a process of active secretion which needs metabolic energy and is not based on a filtration-reabsorption mechanism. Magee (99) reports that the production of cholic acid varies directly with the logarithm of molar amounts of L-essential amino acids added to the diet. The amount of cholic acid produced from a given weight of casein can be accounted for by the millimoles of essential amino acids it contains.

For those interested in the physical properties of bile and the interrelationship between bile salts and cholesterol the following references are of value: (100, 101).

Gall bladder.—Hoppe (102) points out that the ideal chemical structure of a compound for Roentgenographic visualization of the gall bladder should consist of two parts: first, an iodinated aromatic nucleus to provide radio opacity, and second, an optimum balance between lipophilic and hydrophilic properties to ensure absorption following oral administration and direct excretion into the bile. He found that optimum gall bladder visualization was observed with a seven carbon side chain among the di-iodo series and with a five carbon side chain attached to a tri-iodo-aromatic nucleus. Of the many compounds studied the most effective and least toxic oral cholecystographic medium was found to be 3-(3-amino-2, 4, 6-tri-iodophenyl)-2-ethylpropanoic acid (iodopanoic acid telepaque). This is an important problem with many possibilities for further investigation.

Duncan and his associates (103) find that pancreozymin injected intravenously in doses of 2.0 to 2.5 mg./kilo of body weight produces gall baldder contraction in human subjects within 3 to 5 min.; maximum contractions are present in 8 to 12 min. Snape & Friedman (104) report that in dogs and man the choledocho-duodenal sphincter just proximal to the sphincter of Oddi is essentially the organ which prevents the reflex of intestinal contents into the biliary tract. Active contraction of the gall bladder will not result in its evacuation if there is not also a relaxation of the sphincter. Acid gastric juice in the intestine is adequate to produce such relaxation. This may be the mechanism of cholecystokinin action.

Pancreas

Factors influencing pancreatic secretion.—Richman *et al.* (105) studied pancreatic secretory responses in dogs with duodenal fistulae before and after subtotal gastrectomy. They noted that after the gastric resection there was no significant change in the ability of the pancreas to respond to a standard dose of secretin, but that after a standard meal the pancreatic secretions were diminished. The percentage decreases are as follows: volume, 65 per cent, amylase output 68 per cent, and bicarbonate concentration 38 per cent. After a standard dose of histamine the decreases were as follows:

volume 61 per cent, amylase output 67 per cent, and bicarbonate concentration 18 per cent. The authors suggest subtotal gastrectomy in the treatment of chronic recurrent pancreatitis.

The importance of a pancreatic function test in man to determine the severity of acute pancreatitis and the relation of pancreatic secretion to various digestive disorders is discussed by Dreiling (106). The test he introduces requires the insertion of a double lumened gastroduodenal tube for collection of gastric and duodenal drainage. After a control collection period of 20 min., 1.0 clinical-unit of secretin/kilo is given intravenously and collections are made again at 20 min. intervals for a total of 80 min. The duodenal samples are then examined for volume, $NaHCO_3$ and amylase concentration.

To study experimental pancreatic deficiency and factors that would relieve the symptoms of the same, Dragstedt *et al.* (107) prepared dogs with ligated pancreatic ducts. The results obtained, which confirm a previous report, show that autoclaved beef pancreas was effective in relieving and preventing fatty infiltration of the liver as well as other manifestations of lipiocaic deficiencies in deprancreatized dogs. Autoclaved liver, brains, and salivary glands were without effect. The principle in the beef pancreas is relatively heat resistant, and it is not trypsin or any of the known pancreatic enzymes. The fact that liver, brain, and salivary glands did not show any effect indicates that the active principle is not a known lipotropic agent such as choline, methionine, inosital, or a combination of them.

Mention should also be made of the reports available on the effects of autonomic drugs on pancreatic secretion (108, 109, 110), as well as the inhibitory effect of carbonic anhydrase (111) and the experimental production of acute pancreatitis with ethiomine (112, 113).

Properties of pancreatic cells and enzyme action.—Verne & Hebert (114) studied the cytological changes of the pancreas of rats following protein-deficient diets. After the body weight had dropped 20 to 25 per cent they recorded a marked decrease in the size of the pancreas, a progressive disappearance of secretory granules, and collapse of the acinar cells. This, along with the observations of Wachstein & Meisel (115) and Allfrey *et al.* (116), gives evidence that protein components of nucleoproteins are necessary precursors for protein synthesis in the pancreas.

To determine the amylase content of pancreatic juice, Guth and his associates (117) used a modification of the phototurbidimetric method of Waldron. The results indicated a constancy of the ratio of amylase to protein nitrogen concentration. Hokin & Hokin (118) noted that when enzyme secretion is stimulated in pancreas slices with cholenergic drugs the rate of incorporation of P^{32} into the total phospholipids is 4 to 12 times greater than that of the unstimulated slices. This mechanism is abolished by atropine. Clement & Clement (119) noted that juice collected directly from the pancreatic duct of rats six to eight months of age showed a considerable but quite variable ability to esterify cholesterol and to hydrolyze a phosphatide mixture isolated from the liver. These enzymes were inactivated when the juice was heated for 1 hr. at 56°C. Komarov and his associates (120) showed

a high degree of correlation between proteolytic or lipolytic activity of dog pancreatic secretions and its protein nitrogen content. However, any correlation between total enzyme concentration in pancreatic juice and protein nitrogen was very variable.

Small Intestine

Motility.—Foulk *et al.* (121) deserve considerable credit for establishing a pattern for quantitative analysis of motility and basic rhythm in the duodenum and upper part of the jejunum of human beings, such as we now have for the stomach and large intestine. The method consisted in passing a small rubber balloon attached to a tube via the mouth into the duodenum or upper part of the jejunum. The exact location of the balloon was verified by x-ray. When in position, the balloon was filled with 15 cc. of H_2O and then connected to a glass spoon manometer. The wave patterns recorded were classified as types I and III. Measurements of these waves and their frequency were made and the percentage of the observation time during which activity was present was also determined in each record. In all the records, periods of activity alternated with period of quiescence. When normal persons fasted over night, motility was present 60 to 70 per cent of the time, which was reduced to 34 per cent by a fast of 24 to 36 hrs. During the active periods, type I waves occurred almost continuously and type III waves were seen about half the time. Bursts of type I waves in rhythmic sequence occupied about 2 per cent of the tracings for normal and duodenal ulcer patients. In patients with ulcerative colitis these bursts of type I waves occupied 6 per cent of the tracing. Type I waves always occurred at a mean rate of 11/min. The authors consider the rate of rhythmic type I waves to be the basic rhythm of the small intestine.

With reference to factors that alter intestinal motility we have the following observations: Roth *et al.* (122) on emotional factors; Elwell & Bean (123) on the action of curare on motility and vascularity; Bulbring (124) on the interrelationship of O_2 consumption and mechanical changes in smooth muscle; Lungholm (125) on the adrenalin effect; Janowitz *et al.* (126) on the effects of "Tween 65" and "Tween 80"; Weinberg (127), Chen & Portman (128), and Freedman & Hollenbeck (129) on blocking effects of different drugs; and, finally, Feldberg & Smith (130) on histamine-liberating drugs. These papers are all worthy of discussion, but space will not allow any elaboration.

Likewise, relative to propulsive motility studies we refer to the effects of nicotine by Stickney *et al.* (131), the combined effects of tetraethylammonium chloride and hypoxia by Fang, Northup & Van Liere (132), and Banthine action by Nasio (133).

Intestinal Secretions and Absorption

Secretion.—Vitale *et al.* (134) point out that the intestinal mucosa is one of the more active metabolic tissues of the body. They report that subcutaneous injections of aminopterin or 4-amino folic acid has a marked effect on

the O_2 utilization by the mucosa cells. The normal O_2 utilization is approximately 12 to 16 microliters per mg. per hr., and within an hour after the injection there is a marked drop in the rate of O_2 uptake. The morphologic changes present tagged behind the metabolic changes and were most marked after the fourth day. When the respiration rate of the villus tip epithelium was lowest there was almost complete absence of normal mitotic activity. When respiration rate started to increase the mitosis also returned.

Concerning the passage of ions, or secretion, into the lumen of the intestine, a number of observations have been reported. Causeret (135) showed that increased fluid ingestion by the rat caused an increase in urinary and fecal excretion of dietary calcium. Thomas and his associates, using radio calcium[45], (136) noted that rabbits fed continuouly on spinach for 7 to 18 days lost calcium from the blood and excreted it in the feces at an increased rate. The rate of uptake of the radio calcium by the bones was also decreased, as was the urinary excretion of calcium. The injection by stomach tube of 1250 to 3750 mg. of sodium versene gave the same results as spinach. The excretion of chlorides into the small intestine of cattle was noted after the intravenous injection of hypertonic solutions.

Lesser & Pareira (137) in making a study of the relationship of electrolyte composition of gastrointestinal secretions to bowel function, showed that during a loss of tone for two or three days the amount of major electrolytes, such as Na, K, Cl, and HCO_3, in the small and large intestine decreased. This relation does not hold in the case of the stomach.

Carbohydrate absorption.—Wilson & Wiseman (138) describe a method whereby they ligated at both ends an everted piece of small intestine, and filled the sac with sufficient fluid to distend the wall. This afforded a convenient preparation for measuring the effects of adequate and inadequate oxygenation on the active transference of substances across the wall from the bath in which the sac was suspended. The results show that under aerobic conditions, water, glucose, and methionine moved into the sac against a concentration gradient, while under anaerobic conditions water was lost from the sac and no active transfer occurred. In the intestinal sac of the rat they observed that the majority of glucose absorbed appears as lactate.

Fat absorption.—Pessoa, Kim & Ivy (139) report on the absorption of neutral fat and its constituent free fatty acids in normal, biliary fistula, and pancreatic duct ligated dogs. They show that 70 per cent of neutral fat, such as corn oil, and 55 to 75 per cent of corn oil-fatty acids of oleic acid is absorbed in the absence of bile or pancreatic juice. This shows that neither bile nor pancreatic juice is indispensable for the absorption of any of the fats and fatty acids studied. Low melting point fats are better absorbed than high melting point fats. Bernhard & Ritzel (140) also noted that fat can be absorbed in the absence of bile. They find that under these conditions the dietary fat in the intestine is diluted by endogenous fat secreted into the lumen of the intestine. Singer *et al.* (141) report on coconut and olive oil absorption in dogs with Thiry fistulas. They too found that bile salts and pancreatic lipase are not necessary for particulate fat absorption. The chylomico-

graph resulting from fat absorption from the Thiry fistula is described; also a new particle named enterolipomicron, which may possibly represent the form in which fat is secreted into the lumen of the intestine. Favarger & Gerlach (142) report experiments in which mixtures of fats and free fatty acids are fed to rats; samples collected from various areas of the intestine are analyzed for the presence of free fatty acid, glycerides, and phospholipids. The results show that the distribution of fatty acids throughout the intestine varied with the nature of the acids and composition of the mixtures fed. This difference was less marked with the phospholipids than with the glycerides.

Ward, Haslam & Schiff (143) kept one group of rats on choline-free diets for 72 days, another for 225 days, and still another on the same diet plus 15 mg. of choline/rat/day, to find what effect the resulting damage to the liver would have on the absorption of fat from the intestine. The results show that the liver damage does not affect the rate of absorption of cottonseed oil, the degree of hydrolysis of fat in the intestine, or the level of serum lipids. The manner in which phospholipids are absorbed from the intestine is described by Bloom and his associates (144). To unanesthetized rats provided with intestinal lymphatic fistulae labeled phospholipids or triglycerides were fed. Far greater amounts of phospholipids were found in the lymph than of triglycerides. The authors confirm that a significant portion of fed phospholipids are absorbed before they undergo complete hydrolysis.

Protein absorption.—To study the active absorption of amino acids by the intestine, Agar *et al.* (145) used isolated rats' intestine loops. They placed 50 cc. of Krebs' bicarbonate solution previously gassed with 5 per cent CO_2 and O_2 both inside and outside of the loop. The solutions also contained 5 mg./cc. of glucose. Various aminoacids or peptides were added either to the inner fluid only or to both fluids, and the concentration changes were recorded. They found that the L but not the D isomers of histidine and phenylalanine and glutamic acid crossed the intestine against a gradient. Although peptides, glycylglycine, and L-leucylglycine underwent considerable hydrolysis during the experiment definite fractions were transferred intact. Noll (146) using an electrometric device for studying tryptic digestion of various proteins found that the presence of bile salts improves only the tryptic digestion of hemoglobin. Wild *et al.* (147) found that amino acid mixtures were less rapidly absorbed by old persons than those of average age, as indicated by a less marked elevation of aminoacids in the blood after oral administration.

Water and mineral absorption.—Donnet & Garnier (148) gave daily subcutaneous injections of progesterone and estradiol to female dogs for one week. They then recorded the rate of absorption of water from intestinal loops and noted a marked increase. Visscher (149), in reviewing the factors involved in the transfer of electrolytes and water across the intestinal wall, points out that intestinal mobility plays a large part in determining the functional activity of ion-exchange resins. Wissler *et al.* (150) studied the effect of the emulsifying agent "Tween 20" on the intestinal absorption of

iron in hamsters. They noted that after Tween was fed for 8 to 20 weeks there was a consistent increase in the absorption of a test dose of radioactive iron "Fe^{59}". The deposits of iron were greatest in the areas known to be damaged by prolonged treatment with "Tween 20." Fournier *et al.* (151) report on the fate of phosphorus in various parts of the digestive tract in the adult rat. Alimentary phosphorus is regularly absorbed in the stomach and small intestine. In the small intestine endogenous phosphorus often masks the absorption of alimentary phosphorus. There is no absorption of phosphorus in the colon. Cordier & Piery (152) recorded that intestinal absorption of inorganic phosphate was accelerated by breathing air containing 20 per cent CO_2 and strongly retarded by anoxia, traumatic shock, or toxic doses of histamine.

Vitamin absorption.—Quick, Hussey & Collentine (153) report on the vitamin K requirement in dogs to maintain the prothrombin level of the blood normal, and also the relation of bile to the absorption of vitamin K from the intestine. They used dogs with the cholecystonephrostomy operation, because loss of bile through the kidney decreases the absorption of vitamin K and also allows for the production of a severe hypoprothrombinemia. The results show that .5 μg. of vitamin K/kg. of body weight/day is required to maintain normal prothrombin levels. With large doses of bile 5 ml./kilo of body weight/day is sufficient to cause vitamin K to be absorbed from the diet to restore normal concentrations of prothrombin. Kano and his associates (154) suggest that the ability of iodinated casein to increase the sensitivity of chicks to dietary vitamin B_{12} is in part attributable to an interference with intestinal absorption of the vitamin.

Colon

Motility.—Recio & Oppenheimer (155) deserve considerable credit for a comprehensive study on the effects of altered acid-base balance on the physiologic and pharmacologic behavior of the colon in unanesthetized dogs. They record colonic pressure and activity patterns simultaneously in the proximal and distal colon and note the effect of induced acidosis by intravenous injections of ammonium chloride. Normal rhythmic activity was present about two-thirds of the time, but following the onset of mild or severe acidosis there was a marked reduction in all types of activity. The administration of excitatory and inhibitory drugs during normal and acidotic states are also reported.

Debray and his associates (156) studied graphically the presence of a reflex originating upon stimulation of the anus, and resulting in a sudden interruption of contractions of the rectum and the sigmoid within 30 to 60 sec. and lasting for 1 to 3 min. They gave it the name "ano-sigmoidal inhibitory reflex." The authors discuss its importance in physiological regulation of rectal continence; under pathological conditions its persistence may be responsible for certain types of constipation. Floyd & Walls (157) studied the nature of the external and sphincter muscles in man. By means of silver-silver chloride electrodes applied to the skin on each side of the anal aperture

the tone of the sphincter could be recorded electromyographically. The results show that the sphincter is always in a tonic state during waking hours with a wide range of variation in different subjects. They also noted that intra-abdominal pressure is always accompanied by increase in sphincter tone, except during the straining for defecation, when the tone is decreased. The authors noted also two types of muscle fibers (red and white) in external sphincter muscles.

Absorption and excretion.—After injecting ascorbic acid into rabbit lower colon in the form of cacao butter suppositories Azorim (158) found a definite increase of ascorbic acid in the blood stream within 3 hr., the amounts recorded being proportional to the dose used. Cremer *et al.* (159) report that the absorption of calcium from the rectum is very slight.

Forsyth and his associates (160) point out the variability of fecal nitrogen excretion with liquid and solid diets. The results obtained on 26 patients on the two different diets definitely indicate that with nitrogen balance studies one should not assume the fecal nitrogen to be 10 per cent of the nitrogen intake as is often done. Magee, Kim & Ivy (161) studied the effect of dietary protein on the fat content of feces in dogs and rats. In certain basal diets containing considerable amounts of fat the level of fecal fat was established. When casein was added to the diet the fecal fat content was decreased. Supposedly the added casein stimulates the production of bile acids and thus allows a better absorption of fat in the intestine. They also suggest the possibility that the increased protein intake may increase the output of pancreatic lipase and thus facilitate fat digestion. Magee (162) in a more recent work questions this interpretation. He points out that both gelatin and casein will decrease fecal fat, while one does not increase the bile cholate, and the other does. Cohen & Annegus (163) report that dogs, without pancreatic juice, allow 35 per cent of dietary cornstarch to be lost in the feces, 40 per cent of dietary horsemeat nitrogen, and 40 per cent of dietary lard, as well as some oleic acid. The authors also noted that added $NaHCO_3$ reduces the fecal loss of oleic acid in normal dogs.

Constipation and diarrhea.—Porges (164) discusses dietetic treatment of constipation and points out that the chemical stimuli that relieve constipation are organic acids produced out of carbohydrates by fermenting bacteria in the colon. He suggests that laxative foods contain carbohydrates protected by cellulose from being absorbed in the small intestine. Marks (165) reviewing the various available laxatives and their qualifications points out that dioxyanthraquinone (Dorbane) has been used very successfully in the treatment of various types of functional constipation. Banner (166) discusses the use of rectal suppositories instead of enemas in the postpartum period. The suppository used was found to liberate a certain amount of carbon dioxide gas, which is said to have a stimulating influence on peristaltic and defecation reflexes.

Fradkin (167) reports the use of carob flour, hydroscopic fruit powder, with good results in the chronic diarrheas of adults exclusive of etiology. The use of this preparation does not impair the absorption of chloramphenicol

(chloromycetin), oxytetracycline (terramycin), or chlortetracycline (aureomycin).

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PERIPHERAL CIRCULATION[1,2]

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Methods

From the volume pulse of the finger tip, with and without graded venous occlusion, the rate of volume change and of inflow and the rate of outflow (by difference) have been deduced. It follows that outflow in small veins should be pulsatile, having a maximum just after the inflow maximum (1). Whether the pulsewave is transmitted across the capillaries or directly from small arteries to small veins remains to be seen. The main difficulties in such an evaluation arise from the small capacity of the venous vascular bed in the finger tip (2) and the necessity of a quantitative elimination of the occlusion artefact. In a pressure plethysmograph, adapted for venous occlusion measurements, flow diminishes if positive or negative pressures are applied (3, 4). Critical closing pressures corresponding to variations of arteriolar tone can be measured.

A kind of positive pressure plethysmography has been used to obtain information on the function of the arteriovenous anastomoses (5 to 8). These authors recorded the modifications of an arbitrary set external mean pressure by the pressure in the vessels of the enclosed limb. When this mean external pressure corresponds to an assumed mean capillary or venous pressure, they identify the records obtained with "capillary" and "venous" pressures respectively, assuming that the pressures in those vessels, whose walls have been rendered tensionless by external pressure, are electively transmitted to the plethysmograph. It seems advisable to realize that a close relation of the pressures thus recorded to the corresponding pressures in the undisturbed circulation can not necessarily be expected. It is very likely that the external pressure applied modifies the circulation and that the low pressures are influenced by the capacity and pressure variations of vessels with higher pressures when the plethysmograph is pressurized. The conclusions drawn as to the function of arteriovenous anastomoses have been criticized (9). The volume of blood which a human forearm, previously rendered bloodless by applying high external pressure, will take up in a pressure plethysmograph on release of the circulation has been correlated with different values of mean external pressures applied. It can be shown that most of the blood could be prevented from entering the forearm by pressures just above venous pressure. A baseline venous volume could thus be determined corresponding to an effective venous pressure just exceeding zero, and further increase in

[1] The survey of the literature to which this review pertains was concluded in June 1954.

[2] The following abbreviations have been used in this chapter: PAH (para-aminohippuric acid); H.T. (5-hydroxytryptamine); EEG (electroencephalogram).

volume could be correlated to positive values of effective venous pressure (10).

The mercury-in-rubber strain gauge, formerly used for recording respiration (11), has been revived and adapted to venous occlusion plethysmography (12) and to the recording of aortic diameter in animals (13). Blood flow and blood volume in the human forearm has been estimated by constant speed intra-arterial infusion of T1824 and sampling in different veins (14).

The arterial pulse in humans has been recorded with a sensitive infrasound microphone (15). For use in clinical diagnostics, changes of conductivity in a high frequency a.c. field reflecting volume changes of arteries in human limbs have been recorded (16). Auscultatory blood pressure measurements in humans at rest and at work have been checked against direct intra-arterial measurements (17). The view that there could be large differences in either direction in brachial pressure measured by the auscultatory method in case of altered haemodynamics peripheral to the point of measurement has been, let us hope, definitively disproved by comparison with direct intra-arterial recording. Such differences either result from faulty measurements or they reflect conditions proximal to the point of measurement (18).

By mathematical analysis yielding multiple regression coefficients, data obtained by inducing pulsating blood flow in human cadavers have been so arranged as to yield a simple formula correlating stroke volume with pulse pressure, diastolic pressure, and age. Including data pertinent to "*Windkessel*" function such as pulse wave velocity and body length did not conspicuously improve this correlation (19). This formula correlates well with data from nitrous oxide and acetylene methods for cardiac output determinations but gives lower values compared with the direct Fick and dye dilution methods (20). Several papers are concerned with the adaptation of the dye dilution method for cardiac output to continuous recording with a photoelectric densitometer (21, 22, 23). A method for evaluating sample data has also been described (24). The influence of the injection site has been tested in animal experiments (25, 26). In experiments involving hypoxia the dye dilution method has proven superior to the direct Fick, because arterial HbO_2 content never becomes quite constant in such experiments (27, 28). An analysis of possible errors of the Fick principle in the presence of cyclic variations of the measured values has been given (29). The oxygen content of the pulmonary arterial blood has been found not to change much during various phases of the respiratory and cardiac cycle (30). Continuous constant speed injection of T1824 into the ascending aorta, and sampling in a peripheral artery before recirculation begins, allows a fair estimate of cardiac output (31). An attempt to calculate regional contributions to cardiac output by evaluating regional venous PAH^2 concentrations during continuous infusion had to be given up, as there was no adequate mixing in the great veins because of a laminar blood flow (32). A technique for calculating cardiac output from data obtained by sampling arterial blood during and after a constant intravenous infusion of PAH has been described (33).

Balloon catheter methods have been used in humans (34) and in animals (35) for the purpose of temporarily obstructing various vessels. For blood volume studies, red corpuscles have been labelled with thorium B (36), radio-chromium (37) and P^{32} (38).

For animal experiments several new flowmeters have been described: flowmeter using thermistors (39), the density flowmeter (40), and another automatic Ludwig stromuhr (41) measure mean volume flow. A modified Bristle flowmeter (42, 43), a differential strain gauge manometer (44), and an electronic version of Chauveau's hemodrometer (45) may be useful for recording phasic flow. The conditions under which the Rein thermostromuhr can be used for quantitative blood flow measurements have been investigated (46, 47). The Gibbs method for measuring blood flow in cerebral tissue has been modified by use of resistance thermometers (48). Grayson's method for measuring liver blood flow with heated thermocouples has been criticized and found suitable for qualitative measurements only (49).

A systematic error in the method of recording dog's blood pressure in a carotid artery loop has been eliminated by adding an empirically determined correction factor (50). Several methods for recording blood pressure in small laboratory animals have been published (51 to 57). A new blood pressure stabilizer (55) and a new perfusion apparatus for organs of the cat (56) have been described. The weight of the spleen (57) and that of a loop of intestine (58) have been continuously recorded.

General Haemodynamic Considerations

Arteries.—Dynamic elasticity, viscosity, and thermoelastic behaviour of the aortic wall have been studied and compared with a number of rubber-like materials (59).

Several attempts have been made to measure directly the elasticity coefficient E' in the intact circulation. By means of injections with a piston pump, slow periodic volume changes are imposed on the arterial system of narcotized dogs. E' has been calculated by comparing the diastolic slope of individual pulse curves (60). It could be shown that the distensibility $1/E'$ of the arterial system is diminished when vascular tone is augmented (61). This observation contrasts with older estimates based on measurements of pulse wave velocity. Direct measurements of the pressure-volume diagram of a temporarily isolated segment of the dog's aorta showed increased distensibility after epinephrine (adrenaline) in the lower pressure range (62). The difference may be reconciled by considering that adrenergic vasoconstriction may decrease the "*Windkessel*" volume of the intact circulation by action on the large arteries which contribute more than 75 per cent to the volume of the arterial tree. In the cat the drop of arterial pressure after compression of the thoracic aorta has been recorded with an elastic manometer, with and without an additional mercury manometer. As the difference between the two curves is attributable to the known volume of blood displaced into the mercury manometer, the pressure-volume relationship of the peripheral ar-

terial tree could be calculated (63). By a rather indirect method, using a record of the central pressure pulse, a determination of pulse wave velocity, and of cardiac output by the dye dilution method, one can venture to calculate the distensibility of the arterial system in man (64). The same recording may allow calculating stroke volume from beat to beat after one determination with the dye dilution method (65).

To the Poiseuille equation one corrective expression has been added taking account of the fact that the radii even of the small vessels are, because of the distensibility, a function of pressure. The resulting formula yields most of the known properties of pressure-flow relationship, such as concavity towards the pressure axis and the intercepts on the pressure axis at positive pressures. Less importance has been attached to changes of viscosity (66). By means of a pulser device supplying a known constant force pattern, artificial pulses have been induced in the dog's arterial system which can be compared with the pulses induced by the unknown force pattern of the heart beat. The differences in shape of the artificial constant stroke volume pulses under varying conditions of the circulation stress the difficulties of calculating stroke volume from pulse contour data. It could be shown that in pulsating flow three parameters are involved: the pressure manifested by the product of mass and acceleration, by viscous friction, and by wall tension. Vascular pressure is considered to be effectively the sum of these three forces which vary in a nonlinear manner. The ascent of the pulse contour is mainly determined by a combination of the first two factors termed acceleration transient, the pressure effect of which can be shown to be minimal at a normal arterial pressure. No quantitative evaluation of the data has yet been attempted (67).

Blood flow in the dog's femoral artery has been calculated from pressure gradients obtained by recording pulse pressures simultaneously at two points along the artery, using a formula devised for calculating flow from oscillating pressure gradients (68, 69). The results have been compared with data obtained by recording movements of small air bubbles in that artery by means of high speed cinematography (70). Good agreement has been found and systolic backflow established.

A mechanical analysis of the arterial pulse wave in an "*Windkesselmodell*" has been made (71). The variations of intimal thickness are shown to have a great influence on the percentage shortening of ring muscles necessary to obliterate the vascular lumen (72).

The hemodynamic influence of a bend in a pipeline (73) and that of a partially stenotic collapsible vessel (74) have been investigated. A mathematical analysis has been made of the effect of a localized sudden change in tube diameter (75) and of the changes of flow in a branching circulation resulting from active change of diameter in one section of the vascular bed (76).

Capillaries.—A theory of capillary permeability has been established and reviewed (77). While the whole endothelial surface is available for the passage of oxygen, carbon dioxide, and other molecules soluble in lipids and

water, water- and lipid-insoluble molecules can only pass through aqueous pores penetrating the capillary wall. These pores have molecular dimensions of from 30 to 45 Å, and their cross-sectional area comprises less than 0.2 per cent of the capillary surface; they may well be limited to the areas between endothelial cells. While hydrodynamic flow through these pores is rather slow (less than 2 per cent of plasma flow) diffusion of small molecules through them may be very rapid at rates of from 10 to 80 times the rate at which these substances are brought to the tissues by filtration alone. Diffusion, however, through these pores is restricted according to size and shape of the molecules concerned, the degree of molecular sieving depending on the ratio of the molecules' restricted diffusion coefficient to the rate of hydrodynamic flow through the capillary wall. It follows that at high filtration rates even small molecules may be sieved, while even large protein molecules may approach equilibrium with the ultrafiltrate at abnormally low filtration rates.

Studies of the permeability of capillaries in the isolated hind paws of the cat to lipid-soluble and lipid-insoluble substances are in agreement with the above theory (78). The same applies to studies of the filtration rate of different plasma proteins in the human forearm using the Landis technique (79).

Several papers are concerned with the effect of cortisone on capillary permeability in animals (80) and in humans (81), and with permeability in allergic diseases (82). According to experiments using a fluorescein-labelled bovine albumin conjugate, capillary permeability is not a prominent factor in irreversible hemorrhagic shock (83).

The more clinical aspects of capillary function have been reviewed (84). A mathematical analysis of the time course of capillary exchange has been given (85). In the capillaries of the interdigital membrane of the frog the number of passing erythrocytes have been counted with a photomultiplier and correlated to the measured vascular diameter (86).

Veins.—Mean circulatory pressure is a fictitious value arrived at if one imagines all circulatory movements stopped and pressures equalized. Attempts to measure it by stopping the heart have been made (87). In the human a local mean circulatory filling pressure can be measured by recording venous pressure in an extremity excluded from the circulation by sudden inflation of a pneumatic cuff. It could be shown that arterial and venous pressures equilibrate in less than one minute and that the resulting pressure, low in cases of shock, rather high in cases with congestive failure, behaves as if possibly correlated with a general mean circulatory filling pressure (88). This should, however, not be sufficient reason to call this value the "intrinsic blood pressure."

The search for receptors controlling fluid volume continued. Experiments failed to demonstrate any influence of increased intracranial venous volume on renal hemodynamics and function (91). However, such receptors may exist within the thoracic circulation, as continuous negative pressure breathing influences renal water excretion (89, 90).

If the right atrium of a dog is fed by a constant volume pump working

from a reservoir to which the flow of both vaene cavae has been diverted, increase in arterial pressure indicating rise in total peripheral resistance is always associated with increase in venous return, indicating that the capacity of postarteriolar vessels changes parallel to and coordinated with arteriolar tone (92). This would indicate absence of shock and is contrary to current experience in perfusion experiments. If the heart of a living dog is replaced by Dale-Schuster pumps supplying both pulmonary and systemic circulation, the animal is apt to enter a condition of peripheral circulatory shock with vasoconstriction and pooling of blood in the splanchnic vessels, though respiratory and circulatory reflexes are still working (93). Shock is less likely to occur in sheep perfused in the same way by constant volume Dale-Schuster pumps. In this preparation, changes in vena cava pressure resulting from active venoconstriction can be differentiated from those caused by the heart or attributable to changes in the ratio of blood volume to vascular capacity. Digitalis can induce venoconstriction. So does epinephrine and norepinephrine, while papaverine relaxes venous tone (94).

The flow in the thoracic part of vena cava inferior of the dog has been recorded with a differential strain gauge manometer. Predominantly systolic acceleration occurs only with very high pulse frequency or with diminished venous return; normally, and in bradycardia, diastolic acceleration prevails; there is always a deceleration during atrial systole (44). By use of a bristle flow meter essentially the same results have been obtained, but more weight is attached to systolic acceleration in tachycardia (95).

By measuring vena cava superior blood flow in the dog with a Pitot head-type flow meter, an increase in venous return after the change from intermittent positive pressure to alternating positive-negative pressure breathing has been demonstrated (96, 97).

The distensibility characteristics of the portal vascular bed have been examined by injection from the venous side of an intestinal loop temporarily isolated from the circulation. Adrenergic stimulation increases distensibility, provided there is enough distension to counteract the Laplacian effect of diminished vascular diameter (62). Pressures in very small veins are an interesting subject, especially as the question is still open concerning how far arteriolar pulsation by rhythmic compression may help unidirectional venous flow (98). Small catheters have been introduced in a retrograde direction in small veins in the dog's pad. Small cyclic variations similar to waves in arteries have been observed (99), but one must question how much the presence of the catheter will influence pressure and flow.

Nervous Control

Recent investigations have focussed increasing interest on a number of cortical areas from which cardiovascular and respiratory effects have been elicited by electrical stimulation. Arterial pressure responses have been produced by stimulating the posterior orbital surface, the temporal pole, and

the anterior insula in the monkey. Retrogasserian neurectomy did not alter these effects (100). In the human the excitability characteristics of these cortical areas have been investigated prior to lobectomy. The uncus and the motor cortex differ in terms of intensity/frequency relationship (101). In unanesthetized cats arterial pressure responses have been obtained from stimulation of the pyramidal tract. It is concluded that the cerebral cortex can effectively influence most autonomic functions by direct action on the spinal cord, separately from the hypothalmus and its descending paths (102).

Cerebral cortical ablations, however, did not influence the arterial pressure of experimental hypertensive dogs (103), nor did destruction of the hypothalamus and its descending pathway permanently influence arterial pressure in neurogenic hypertension (104). Venous occlusion plethysmography in human limbs employing ganglionic blocking agents produced no evidence of increased neurogenic vasomotor tone in patients with essential hypertension (105).

Vasodilatation in skeletal muscles has been produced by stimulation of two regions in the distal part of the rhomboid fossa (106). Stimulation of an area close to the midline caused bilateral vasodilatation resulting from inhibition of vasoconstrictor tone presumably by exciting fibres mediating inhibitory vagus and sinus nerve impulses to vasoconstrictor neurons (107). Stimulation of the ventrolateral part of the medulla produced ipsilateral vasodilatation which could be blocked by atropine and which was assumed to be attributable to cholinergic sympathetic vasodilator fibres constituting the bulbar extension of a corticohypothalamicomesencephalic pathway, which may be concerned in regulating muscle blood flow during activity (108).

Five different baroreceptor areas associated with the right common carotid artery in the cat have been localized (109). There are further reports on the local action of drugs influencing pressure response by changing smooth muscle tone of the carotid sinus wall (110). Adrenolytic drugs reverse the local action of epinephrine and norepinephrine (111, 112). Local application of epinephrine on the cardio-aortic pressor regions induced fall of blood pressure (113).

The effect of blocking the efferent reflex pathway has been quantitatively tested on the isolated carotid sinus by means of arterial pressure characteristics (114). Pressoreceptors could be shown to adapt to a new pressure level in experimental hypertension induced by splanchnic nerve stimulation (115). Pressure changes induced in the isolated carotid sinus had no direct influence on pulmonary arterial pressure (116).

No specific effect of epinephrine and norepinephrine on chemoreceptors has been found on either local or intracarotid application (117). The action of sodium iodo-acetate on carotid sinus nerve action potentials has been explained by its action on the resynthesis of acetylcholine acting as transmitter substance (118). Acetylcholine itself, when injected into the sinus, sensitizes to physiologic baroreceptor stimuli (119). Injected into an isolated carotid

sinus preparation, acetylcholine provoked increased pressure activity, which was not abolished by atropine (120). Veriloid has been shown not to act on chemoreceptors but to sensitize baroreceptors (121).

Chemoreflexes from the heart and the lungs have been reviewed (122). At least three reflex mechanisms are postulated: (*a*) the coronary chemoreflex (Bezold-Jarisch-effect), a reflex fall of arterial pressure and heart rate induced by injection of certain substances into the coronary circulation, elicited by unknown receptors, some of which must be in the left ventricle of the dog (the afferent pathway of this reflex has been followed (123, 124); (*b*) the pulmonary depressor chemoreflex inducing a fall of heart rate and blood pressure; and (*c*) the pulmonary respiratory chemoreflex, both attributable to action on unknown receptors in the lungs (122). Phenyldiguanidine, the principle substance causing these pulmonary reflexes, has been shown not to stimulate any known atrial, arterial, or pulmonary receptors, but to activate normally quiescent fibres (125). Some vagal fibres formerly (on account of the time relation of their action potentials) thought to arise from nerve endings in the small vessels of the lungs have been shown in fact to originate from the atria (126). Afferent vagal fibres have been differentiated by determining their conduction velocity (127) and by degenerative sections at various levels (128).

Humoral Control

After the identification of serotonin, enteramine, and thrombocytin with 5-hydroxytryptamine, much work has been devoted to the action of this substance. Enough H.T.[2] has been found in platelets which have been shown to absorb H.T. from plasma (129) to account for the serum H.T. content after coagulation (130, 131). The local release of H.T. from platelets after injury may account for the vasoconstrictor component in stopping hemorrhage and also for local vasoconstriction at the site of thrombus formation and embolization. While platelets may be concerned in H.T. transport and perhaps in regulating and keeping down H.T. plasma concentration (129), the actual site of H.T. formation must be elsewhere. H.T. has been found in various organs including the intestinal tract (132) and the brain (133, 134). It is normally excreted in the urine (133). It may be of some significance that much H.T. has been found in the cells of the enterochromaffine system (135, 136). Carcinoid tumors consisting of such cells also contain a high concentration of H.T. (137). Its action on the general circulation is complex and therefore variable. There is a direct vasoconstrictor action, a transient ganglionic blocking action, and a peripheral blocking of adrenergic vasoconstriction (138). Of special interest is the stimulating action of hydroxytryptamine on vagal afferents. Stimulation of pulmonary depressor reflexes, of pulmonary respiratory chemoreflexes (139, 140), and even of slowly adapting pulmonary stretch receptors (141) has been discussed, as well as stimulation of aortic and carotid sinus chemo- and baroreceptors (142) and receptors in the area

supplied by the coronary arteries (139). This may have some bearing on pulmonary and coronary embolism and thrombosis, especially as H.T. seems to be the only substance naturally occurring in the blood known to stimulate some of these afferents. H.T. may release histamine (143) and epinephrine (144) in the intact circulation. The antidiuretic action of H.T. has been attributed to a constriction of vasa afferentia (145, 146) reducing renal blood flow. It can be induced by a much smaller dose than can arterial pressure effects (147). The observation that fish with aglomerular kidneys lack the enterochromaffine cell system has been used to strengthen the argument that regulation of glomerular circulation may be one of the function of that H.T.-producing cell system (147). H.T. action can be inhibited by structural analogues (148, 149) and other substances such as yohimbine, ergot alkaloids (150) lysergacid diethylamide (151), and atropine (152). The possibilities of enzymatic synthesis (153) and inactivation (154, 155) of serotonine have been explored.

The action of epinephrine and norepinephrine on isolated swine arteries could be augmented by amineoxidase inhibitors; this was not possible in dog's arteries (156). Thyroxine also augments the action of epinephrine on swine arteries; there is an optimum thyroxine concentration for vasa vasorum flow in the presence of epinephrine (157).

Four different ways in which epinephrine can evoke arteriolar vasodilatation have been differentiated (158). About 1 per cent of epinephrine continuously infused in man could be recovered in the urine (159). Two humans which pronounced postural hypotension showed diminished urinary excretion of epinephrine and norepinephrine, which did not increase after insulin (160).

Further experimental evidence has been accumulated indicating the existence of a dual secretory mechanism for epinephrine and norepinephrine from the adrenal gland involving differentiated cells (161) and innervation by separate fibres with a different hypothalamic representation (162, 163).

An extensive study has been made of the causes of increased sensitivity of the vascular supply of the completely denervated rabbit's ear to epinephrine and other vasoconstrictor substances. Amineoxidase is not concerned. Acetylcholine and acetylcholinesterase, normally continuously formed in the arterial wall under nervous influence and keeping up a background of vasodilatation, could be shown to disappear completely after denervation in a couple of days. Epinephrine action is thus augmented but can no longer be influenced by atropine and physostigmin (164, 165). The same may occur in the human finger. The esterase involved has been shown to be pseudocholine esterase (166).

Circulatory reactions to hypoglycemia have been studied in the rabbit (167) and in the dog (168). Vasodilatation in hypoglycemia may be attributable to the removal of inhibition which blood glucose normally maintains on choline acetylase.

Neurohypophysectomized dogs showed increased susceptibility to hemorrhage induced by standard procedures. This could be corrected by pitressin injections (169).

Review of the great number of papers concerned with pure pharmacology of the peripheral circulation has not been attempted because of lack of space.

Regional Blood Flow

Brain.—The subject has been reviewed by several authors (170, 171, 172, 215).

By measuring local thermal conductivity on cervical sympathetic stimulation, diminution of blood flow could be shown to occur in the white but not in the gray substance. By direct observation through a brain window pial arteries have been shown to dilate homolaterally and to constrict contralaterally in response to stellate block (173). Changes in the pH of rabbit brain surface in ischemia and anoxia have been recorded and correlated with lactic acid formation and carbon dioxide accumulation (174).

Adrenalectomized rats show marked decrease of cerebral blood flow and oxygen consumption along with reduction of EEG[2] frequency. This can be corrected by adrenocortical extracts and cortisone but not by desoxycorticosterone and minerals (175). In patients with essential hypertension, however, adrenalectomy did not change cerebral blood flow in spite of severe reduction of arterial pressure (176).

Using the perfused isolated cat head, it could be demonstrated that, while survival time after complete ischemia decreased with falling tissue temperatures, recovery time, as judged by reappearance of EEG, had an optimum at temperatures round 30°C. (177). Survival time of cerebral tissue in ischemia depends largely on glucose supply. Low sugar consumption can be correlated with disturbances of cerebral function in man (178). In cats perfused with a simplified half-synthetic blood, cerebral glucose consumption stops but can be restored by adding fresh cat's blood or by including the liver in the perfusion circuit (179).

In spite of the very short survival time of cerebral tissue in case of complete ischemia, the dog brain shows no reactive hypercirculation if blood flow is only moderately reduced by raising cerebrospinal fluid pressure (180). This may be taken as evidence of blood flow in excess of metabolic needs.

The influence of the elasticity coefficient of the cerebrospinal space on cerebral circulation (181) and effective arterial pressure and structure of the arterial wall (182) has been investigated.

The contributions of authors concerned in elucidating the influence of cerebral tumors with increased cerebrospinal fluid pressure on cerebral hemodynamics may be listed (183, 184). A modification of the nitrous oxyde method involving continuous sampling has been described (185).

In controlled hypotension induced by ganglionic blocking agents in the supine position cerebral blood flow in the normal may not decrease at sys-

tolic pressure as low as 55 to 60 mm. Hg (186), though in patients with cerebral vascular disease it is advisable not to lower mean blood pressure to less than 70 mm. Hg (187, 188).

Vigorous bodily exercise may increase cerebral blood flow and oxygen consumption in spite of reduction of pH and nearly unchanged arterial carbon dioxide tension (189). In patients with chronic pulmonary emphysema of moderate severity a good correlation of cerebral blood flow with arterial carbon dioxide tension has been found. In exercise, not the arterial pH, but arterial pCO_2, are relevant to cerebral blood flow (190). The decrease in cerebral blood flow and oxygen consumption with age found by some authors may be attributable to the greater incidence of organic cerebral vascular disease (191, 192). Patients with mere hypertension have normal cerebral blood flow and oxygen consumption (193). They may also show a normal reaction (increase of blood flow with decreased cerebral vascular resistance) to breathing of 5 per cent carbon dioxide, while persons with cerebral arteriosclerosis tend to show no or a diminished response even if resting cerebral blood flow and oxygen consumption are still normal (194). Hypertensive patients also keep cerebral oxygen consumption and cerebral blood flow more or less constant if the blood pressure is drastically lowered by medication (195) and surgical procedures (196).

Lungs.—A cortical ischemia similar to that occasionally observed in the liver and the kidney has been shown to occur in the lungs of anaesthetized animals and has been attributed to a common pattern of vascular supply in these organs (196).

Several papers are concerned with the sensitivity of pulmonary vessels (197, 198) and the bronchial muscles (199) to oxygen. One lung perfused by a donor dog showed vasoconstriction on breathing low oxygen and vasodilatation if perfused with blood of low oxygen content (200). In trained and unnarcotized dogs pulmonary arterial and left atrial pressures were measured with angiostomic cannulas. With low oxygen there was an increase in cardiac output (dye and pulse contour methods) but no evidence of increase in pulmonary vascular resistance (201). Bronchospirographic low oxygen breathing in one lung induced reduction of blood flow and low carbon dioxide in that lung (202). The time course of the development of the increase of resistance by local hypoxia has been invesitgated in the rat (203). In the frog lung the vascular action of carbon dioxide could be shown to be different from that of pH (204).

Several authors have recorded pulmonary arterial "wedge" pressures along with directly measured left atrial pressures. It has been maintained by some that even cyclic variations may correlate (205 to 208). It is questionable whether a human subject undergoing bronchoscopy with transbronchial puncture of the left atrium simultaneously with heart catherization is near a normal basal condition. For recording cyclic variation of the left atrial pulse transesophageal recording seems to be a safer procedure (209). Accord-

ing to a regression coefficient analysis there seems to be no correlation between pulmonary arterial "wedge" pressure and pulmonary arterial pressure, even in mitral stenosis (210).

The effects of temporary unilateral occlusion of the pulmonary artery in the human by the balloon catheter method have been reviewed (211). In man dehydroergotamine markedly increases pulmonary arterial pressure while sodium nitrite and ganglionic blocking agents depress it even in cases of chronic cor pulmonale, showing the importance of a nervous factor in chronic pulmonary hypertension (212). Sheep artificially perfused at a constant rate show an increased pulmonary resistance after epinephrine and norepinephrine (213). In the frog lung norepinephrine contracts both bronchial and vascular muscles, and epinephrine relaxes bronchial muscles, while its action on vascular resistance depends on the initial state of these vessels (214).

No decrease in outflow from a catheter in the coronary sinus has been found in the dog after massive pulmonary embolism (215). A throttle valve action of the atrial musculature on pulmonary veins has been suggested (216). The effect of positive pressure breathing on the pulmonary circulation has been studied in the dog (217, 218). The old question of whether contact time of the blood with alveolar air in the lung capillaries is sufficient for oxygen diffusion has been reconsidered. Comparison of the measured oxygenation time of thin layers of concentrated hemoglobin solutions with the upper limit of the contact time throws some doubt on the possibility of explaining pulmonary gas exchange by mere diffusion (219).

Liver.—The bromsulphalein method has been checked with satisfactory results against direct measurements of hepatic vein blood flow in the dog (220). By guided catheterization of many veins, it has been established that loss of bromsulphalein takes place only in the liver and to a small extent in the kidneys (221). In the dog liver rendered chronically ischemic by various operations, bromsulphalein clearance corresponded to the reduced blood flow, which was taken to indicate unaltered liver function (121). Blood flow in the dog liver conspicuously decreased, but spontaneously recovered after severe hemorrhage (222). Intestinal contractions in the dog decrease blood flow and portal pressure, if there is not a simultaneous rise in systemic blood pressure (223). In the dog, not only a terminal sphincter, but also the whole length of the hepatic veins may constrict (224).

The pathway of the pressoreceptor reflex on splanchnic blood flow in the rat has been further investigated. There exists an additional homoeostatic nonneurogenic mechanism of regulating basal resting hepatic blood flow (225). A factor could be demonstrated in freshly defibrinated rat blood, producing vasoconstriction in the isolated perfused rat liver, which is quickly inactivated by circulating through the liver (226). Augmenting portal blood flow by arterial-portal anastomosis delayed but did not abolish irreversible hemorrhagic shock (227). In patients with Laennec's cirrhosis, portocaval anastomosis decreased liver blood flow, but increased bromsulphalein extrac-

tion and arteriovenous oxygen difference (228). During general anesthesia there is a decrease of both splanchnic oxygen consumption and hepatic blood flow (229).

As ascites formation can be much better induced by stenosis of the thoracic part of vena cava inferior than by portal stenosis, it is most likely that liver lymphatics contribute to ascites formation (230). The clinical results of tying off the hepatic artery and other branches of the celiac axis in patients with Laennec's cirrhosis in order to combat ascites formation and esophageal bleeding are not too encouraging (231, 232). It seems to be established that a minimal supply of arterial blood is necessary for the survival of the liver. On the other hand, there are several, but irregular, collateral pathways which might reestablish hepatic arterial blood flow after ligation of the celiac axis (233, 234). Ligation of the hepatic artery in the Eck fistula dog may produce hepatic coma (235, 236), but some animals survived even this drastic diminution of liver blood supply. Bile flow in the dog seems to depend largely on arterial blood pressure suggesting filtration as a component in bile formation (237). In the rat, regeneration after hemihepatectomy occurs only in the presence of arterial blood supply to the liver (238). Circulation in the normal mammalian liver has been studied by the transillumination technique. Arterial portal, but not arterial venous, anastomosis occurred (239, 240), though the latter are postulated on pharmacological grounds (241). Interlobular branches of hepatic artery have been seen (242).

Kidneys.—The nitrous oxide method for renal blood flow has been compared with the PAH-clearance method (243). Local differences in renal circulation time can be estimated by measuring temperature differences between aortic blood and a set of thermocouples inserted in different parts of the kidney on intra-arterial injections (244). A study of the effect of renin on the renal circulation by means of rapid serial angiography has been made (245).

In the isolated perfused dog kidney, increased vascular resistance at elevated perfusion pressures is associated with a 10 per cent decrease of renal blood volume (246), and not related to increase in "intrarenal pressure" (247). It can be abolished by cyanide poisoning.

Alterations of the pressure-flow relations in the autoperfused dog kidney have been shown to occur after hypophysectomy (248). The decrease of renal blood flow and filtration commonly observed after hypophysectomy has been found to persist in adrenalectomized dogs. It can be partly reversed by injections of thyrotropin and growth hormone (249).

Unilateral splanchnicectomy in anesthetized and unanesthetized dogs produced differences in circulation and filtration of the kidneys which can be explained by loss of sympathetic vascular tone on the operated and increase on the contralateral side. Since these differences diminish during procedures increasing the frequency of pressoreceptor discharge, the crossed stimulation effect is thought to be related to the reflex mechanism of arterial pressure homeostasis (250).

In the human renal tubular transport maxima both for reabsorption and excretion have been found to increase significantly during renal hyperemia induced by aminophylline injection. This may be compatible with the concept that a certain number of nephrons is perfused only during renal vasodilatation (251).

Kidney and hypertension.—On the basis of morphologic observations in experimental hypertensive rats, strong evidence against the possibility of renin formation in the epitheloid cells of the vas afferens and the tubulus contortus I has been obtained, while the Becher cells derived from tubulus contortus II could not be excluded as a possible source of renin (252).

Crude hog renal extracts from the cortex producing elevated antirenin serum titers have been shown to protect dogs against experimental malignant renal hypertension (253); they also lower arterial pressure in spontaneously hypertensive dogs (254). In addition to exerting a pressure effect via hypertensin formation renin may stimulate the anterior pituitary to induce adrenocortical activity (255). A chronic pressure effect persisting for months due to renin or some other vasoactive protein has been obtained in renal hypertensive dogs by injections of crude dog renin (256).

The hypertensinase content of dog plasma has been found decreased 34 per cent two days after nephrectomy, while plasma hypertensinogen showed a threefold increase. Consequently the *in vitro* yield of hypertensin increases when plasma is incubated with small renin concentrations (257). The *in vivo* increased response to renin after nephrectomy does not depend on the nervous system, on sodium intake, nor on the excretory function of the kidney; it appears only several hours after the operation (258). After bilateral adrenalectomy a decrease of renin action results from exhaustion of the available renin substrate (259). Two forms of hypertensin with equal pressure activity have been demonstrated in the plasma by chromatography (260).

By recording the effect of aortic compression on the femoral pulse pressure and mean arterial pressure in the rabbit (261) and the dog (262), no evidence convincing the author of this review could be found which supports the theory that reduction in renal pulse pressure may serve as a stimulus for the development of experimental renal hypertension.

Sodium exchange, controlled by spontaneous intake of water and saline and their output under load, was shown to increase in the early stage of perinephritic and desoxycorticosterone-induced hypertension of rats and to decrease to normal in later stages (263). Corresponding observations could be made on a number of patients with essential hypertension (264). A number of contributions are concerned with the action of various hypotensive drugs in man (265 to 269) and in dogs (270, 271).

Limbs.—Central nervous control of skin vessels, having a low basal tone, seems to be effected only by way of vasoconstrictor fibres, while in the muscles, where vascular tone is much higher, nervous control is exerted in both directions by sympathetic vasoconstrictor as well as dilator fibres (272). Medullary reflexes however can effect vasodilatation in the hind limbs of the dog only by inhibition of sympathetic vasocontrictor activity (273).

That ischemic muscle pain should disappear at a lower cuff pressure than thermic skin pain (274) agrees well with the assumption that skin vessels have a much lower sympathetic tone (and lower closing pressures) than do vessels in muscles. Another difference between the reactions of skin and muscle vessels could be found: while flow in muscles is augmented with every deviation from the physiological pH, skin blood flow increases with falling pH (275).

Almost doubling muscle blood flow by intra-arterial infusion of adenosine-triphosphate, histamine, and acetylcholine in the brachial artery of men does not accelerate repayment of oxygen debt after exercise (276). An increase of blood flow in the human forearm muscles after strenuous exercise has been shown to persist for hours (277), possibly caused by a slowly diffusing metabolite.

The theory that post-contraction hyperemia may be mediated by an axon reflex in cholinergic vasodilator fibres is further strengthened by the observation that it can be abolished by large doses of nicotine. Nicotine could be shown in the cat to set up axon reflexes in sympathetic adrenergic and cholinergic vasodilator fibres, which can also be abolished by large doses of nicotine (278).

Intra-arterial infusions of norepinephrine results in vasoconstriction of forearm muscles, while intravenous norepinephrine brings about increase in forearm flow, which can be abolished by nerve block and sympathectomy (contrary to the corresponding epinephrine effect) (279). In the dog's hind legs, blood flow may be reflexly increased by epinephrine and norepinephrine if injected intravenously or in the aorta, but not if the injection is made distal from the celiac axis. This is considered evidence of norepinephrine-sensitive chemoreceptors in this region (280, 281). It could be demonstrated that both sympathetic and parasympathetic innervation are necessary for the production of the rhythmic contractions of the central artery of the rabbit ear (282).

The increase in blood flow in the human forearm after ultrasonic irradiation has been shown to be attributable to a local thermogenic effect (283). The effect of cyclopropane anesthesia on blood flow in the normal and nerve-blocked human forearm has been studied (284).

Blood flow in the azygos vein draining respiratory muscles has been studied in the dog and found to be well-sustained in hemorrhagic shock (285). Blood draining from the azygos vein can sustain the circulation for some time after tying off both venae cavae (286).

The blood flow through arteriovenous anastomoses in the dog's hind limbs has been estimated by the ball injection method. After denervation more small balls could be recovered (287), while after vagotomy and carotid-sinus denervation fewer balls appeared in the vein (288). No conclusive evidence for the existence of arteriovenous anastomoses in muscle could be obtained (289).

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HEART[1,2]

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The topics, paper selection, and weighting thereof is arbitrary and represents to some extent the interests of the reviewer. During the period covered meetings of the 19th International Physiological Congress and the American Physiological Society took place, as well as many others. These encompass a myriad of papers presumably most of which will appear later *in extenso* and which generally are not considered here.

Electrical Manifestations of Heart Activity

Conduction and excitation.—Prakash (1) studied the minute anatomy of the conducting system of the rat heart. Electrical characteristics of single Purkinje fibres from the heart of the calf, sheep, and kid were determined by Corabœuf & Weidmann (2, 3). In the bovine heart this system contained a specific acetylcholinesterase similar to that in peripheral nerves (4).

The electrical pattern of the frog's atrium approximated that of the ventricular complex (5). In the dog heart the origin of the electrical impulse was found to be located at the head of the sinus node (6). The spread of ventricular activation was studied in the rabbit and cat (7) and in the dog (8). Studies of the form of ventricular activation suggested that the Purkinje tissue acted as a true functional syncitium (9). Scher *et al.* (10) supported the idea of fast endocardial impulse spread followed by syncytial spread through the ventricular wall at a slower rate. A threshold stimulus applied at any myocardial depth in the intact dog's ventricle delayed repolarization during the next few normal beats (11). Spread of ventricular excitation in the dog heart was delayed in bundle branch block (12). Conduction velocity and resting excitability of either ventricular chamber of the dog were greatly elevated by *l*-epinephrine and *l*-norepinephrine and the excitability was not dependent on the associated elevation of serum potassium (13). Digitalis and acute heart failure through aortic ligation had no significant effect on excitability and rhythmicity of the dog heart (14).

Rhythmicity and arrhythmia.—The extent of vagal control of the heart was studied experimentally under different conditions. Reynolds (15, 16) found that resting vagotonia in the heart of the fetal lamb near term was not

[1] The survey of literature pertaining to this review was completed in June, 1954.

[2] The following abbreviations are used: ECG (electrocardiography or electrocardiogram); VCG (vectorcardiography or vectorcardiogram); EKY (electrokymography or electrokymogram); BCG (ballistocardiography or ballistocardiogram); ATP (adenosinetriphosphate); A-V (atrioventricular).

marked, although it was easily induced by circulatory stress, and the earlier positive findings of Barcroft & Barron were explained on this basis. In the adult the degree of vagotonia was found to vary and at least a portion of the effective mechanism lay in change in the repiratory gases. Hypercapnia enhanced vagal arrest in the normal dog but not in the chronic hypoxic dog; acute and chronic hypoxia had no effect, but in one-third of chronically hypoxic dogs ventricular fibrillation was induced by vagal stimulation (17). Local changes related to vagal activity or its equivalent continued to be studied. In line with Gaskell's original discovery (1887) that vagal stimulation increases the potential in arrested turtle hearts, Burgen & Terroux (18) in recording potentials from a single muscle fibre of the cat's atrium found a negative ionotropic effect with application of acetylcholine. In the rabbit's atrium physostigmine in high concentration was found to inhibit contraction by preventing inhibition of cholinesterase, and with its removal contraction returned (19, 20). Vagal escape was ascribed to the disappearance of the increased concentration of sodium in the sino-atrial node which accumulated during vagal stimulation (21).

In clinical studies intrathoracic vagal manipulation and electrical stimulation did not elicit any significant cardiac changes (22). Increased vagal activity was implied from the appearance of intraventricular block and various arrhythmias during intubation and anesthesia (23 to 27) and from the relief obtained with atropine and Banthine in clinical states such as Stokes-Adams seizures with simultaneous atrial and ventricular standstill (28, 29). Of particular interest was the demonstration that external electrical stimulation (pacemaker) resuscitated patients with Stokes-Adams disease from attacks attributable to ventricular standstill, and its continuance appeared to prevent recurrence of irregular ventricular tachycardia (30).

Standardized preparations for the induction and treatment of experimental arrhythmias were explored. Ventricular arrhythmias, tachycardia, flutter, and fibrillation induced in rats by calcium chloride were found to be induced largely through a neurogenic mechanism (31 to 34), while the blocking of arrhythmias induced by aconite by topical application of drugs suggested their cardiogenic basis and an enzymatic approach to the problem. Of a number of drugs tested for their ability to produce reversion to a normal sinus rhythm of the ventricular tachycardia produced in anesthetized dogs by intravenous ouabain, diphenylhydantoin (Dilantine) had the best combination of effectiveness and low toxicity (35). In dogs with ectopic ventricular tachycardia produced by myocardial infarction papaverine exhibited only very mild and brief ectopic impulse-suppressor effect, and dibucaine stopped the ventricular tachycardia of K-strophanthus and decreased mortality (36, 37). Locally liberated potassium was implicated by the same investigator as the excitatory agent in ventricular ectopic activity following acute coronary artery ligation (38).

Other contributions in this field included ionotropic and chronotropic effects of chlortetracycline (aureomycin) in the turtle and frog heart (39);

vagal sensitivity and atrial fibrillation in the hyperthyroid dog (40); effects on systemic blood pressure of ventricular asystole in Stokes-Adams attacks (41); reviews regarding cardiac standstill (42, 43, 44); arrhythmias of aging (45), and classification and treatment of cardiac arrhythmias (46, 47).

Electrocardiography.—High fidelity ECG[2] (48, 49, 50) and telephone transmission with magnetic tape recording (51, 52, 53) were used. Additional contributions regarding experimental and theoretical techniques were concerned with the use of homogeneous torso models (54, 55, 56), electrical field of a given lead (57, 58, 59), potential at an electrode close to the heart (60), zero potential of the heart's electrical field (61, 62, 63), and correspondence of the electrical and anatomical position of the heart (64).

ECG were taken in the mouse (65), cat (66), whale (67), Bantu newborn infant (68), and in the unanesthetized dog (69). In the dog heart no apparent relation was found between the end of systolic ejection and the end of the T wave of the ECG (70). In the same animal the inner ventricular myocardium had little effect on the ECG (71 to 74). Sequential ECG changes in the dog were followed during chronic ligation of the septal artery (75), and after atrial injury induced by cautery, alkali solutions, and by injecting air into the left ventricular cavity (76, 77). Observations were made in a variety of animals of the effect on the ECG of Khellin (78), of adrenal insufficiency associated with hyperpotassemia (79), of infusion of cortisone and related compounds without change in plasma electrolytes (80), of implanted desoxycorticosterone acetate pellets (81), of sympathomimetic drugs on the Q-T interval and on the duration of ejection (82).

The normal human ECG was reviewed (83). ECG patterns were described in hypopotassemia with and without hypocalcemia (84), in funnel chest (85, 86), in hiccups (87), in intravenous veratrum (88), during inhalation of 30 per cent carbon dioxide (89), and in the aging heart without coronary disease (90). In addition there was observed in the ECG a quantitative relation between length of T-P interval and cardiac rate (91, 92); normal variants resembling various types of heart disease (93 to 96); functional abnormalities in normal athletes (97); ST depression in normal young and middle-aged men on exercise (98, 99); primary T wave changes during precordial cooling (100); a negative effect of tobacco smoking per se during hypoxia (101).

Levine (102) re-emphasized the shortcomings of the ECG in the diagnosis of coronary artery disease but observations in a number of papers should be helpful here. Lambert (103) found additional thoracic and abdominal unipolar leads helpful in the diagnosis of myocardial infarction. Heart disease was found to be present in 93 per cent of patients who had inversion of T waves in sinus beats after ventricular extra systoles (104). A lengthened Q-T interval during the Levy anoxemia test was found in almost all patients with true angina pectoris (105) and a definite correlation between the length of the Q-T interval and existence of pathological changes in cardiac musculature in cases of acute myocardial infarction was reported (106). The ECG was a diagnostic aid in coarctation of the aorta in infants (107) and in cerebro-

vascular accidents (108) but not in hemorrhagic fever (109) or in scleroderma (110). Finally, of a large number of drugs tested as vasodilators in coronary artery disease, only glyceryl trinitrate, papaverine, and peritrate were effective in their ability to modify the ECG response to the Master two-step exercise test (111).

Reviews regarding VCG[2] were published by Wolff *et al.* (112) and Burch *et al.* (113, 114). Additional papers were concerned with design and techniques (115 to 119) and with the theoretical and experimental adequacy of this clinical tool (121 to 127). VCG was applied to normal subjects to evaluate heart position (128); QRS-T relation (129, 130, 131); influence of age, build, sex, chest shape (132); pregnancy (133); and various forms of ST depression (134). It was used as a diagnostic aid in mitral stenosis (135), in ventricular hypertrophy (136, 137), and in myocardial infarction (138, 139).

Metabolic Manifestations of Cardiac Activity and Drugs

The physiological properties of washed dog heart muscle and the factors which influenced its work performance were studied. Contractions could only be elicited with ATP[2] in a proper medium (140). Lengthening and shortening of the Q-T interval were generally associated with inhibition and enhancement respectively of ATP activity (141).

Pyruvate and lactate utilization were studied in heart slices (142). Following intraperitoneal injection of labeled bicarbonate into the rat, carbon dioxide fixation by the ventricle was greater than by the atrium (143). Glutamic acid was found to be oxidized by heart homogenates by a mechanism involving transamination with oxalacetic acid and subsequent oxidation of the resulting α-ketoglutaric acid by way of the Krebs cycle (144). A significant decrease was evident in the cytochrome oxidase activity of homogenates of rat and hamster hearts after exposure to anoxia (145). In a comparative study Barron *et al.* (146) found that anaerobic glycolysis which, in the mammalian heart ended with lactic acid formation, in invertebrate hearts produced other acids besides lactic acid. All hearts had a similar oxidative phase, i.e., via the Krebs cycle, and were very sensitive to anoxia. Anoxia also decreased the cardiac glycogen level of goldfish at the time of respiratory failure (147). Evidence is presented in the goldfish, rat, mouse, and dog heart for existence of two forms of glycogen as true physiological entities (148). Additional observations were concerned with the possible usefulness of rubidium as a tracer of potassium in studying the kinetics of myocardial electrolyte turnover in the dog (149) and the development in adrenal insufficiency of a myocardial edema rather than an increase of intracellular fluid (150).

A number of observations were made on myocardial metabolism in the dog and human (151 to 155). For details the reader is referred to original work. However, in general the data showed that the normal heart can extract, use, or store glucose, pyruvate, lactate, fatty acids, ketone bodies, and amino acids, and the extent of use or storage or both depended on the blood

level of the particular substance. In the hypoxic dog, total usage of pyruvate, lactic acid, and glucose was well-maintained to 5 per cent oxygen (152). In patients with high and low output failure, utilization of lactic acid and glucose was not impaired (155). In acute and chronic thiamine-deficiency in dogs, total oxygen and lactic acid usage decreased (151).

The mode of action of the cardiac glycosides was explored in a number of studies. Digitalis intoxication was discussed by DeGraff (156). Potassium-depleted dogs were found by Zeeman *et al.* (157) to have an increased sensitivity to a lethal dose of lanatoside C. Friedman *et al.* (158) presented an excellent review of the behavior and fate of crystalline digitalin (Digitoxin) in the experimental animal and man. In the failing heart-lung preparation, 3-acetyl-strophanthidin produced a positive ionotropic effect comparable to that of ouabain (159). The metabolic pathways for positive ionotropic action of cardiac glycosides were investigated by Ellis (160) with the conclusion that the site of action of K-strophanthus was in an area of metabolism involved in utilization of chemical energy for work. Although C^{14} digitoxin increased respiratory rate in human heart muscle slices, it was believed to act catalytically since no C^{14} oxygen was found (161). Wollenberger (162) found that ouabain accelerated oxidation in dog heart slices of C^{14}-labeled glucose and lactate but not of pyruvate.

Additional observations included the effect of vasodilators upon the dephosphorylating enzymes of the dog's coronary arteries (163); cardiovascular response to rattlesnake venom in the dog (164); and cardiovascular effect of pitressin (165).

Hemodynamic Manifestations of Cardiac Activity

Heart sounds.—Intracardiac sounds were recorded in dog and man (166) by means of a condenser microphone mounted in a catheter tip. A multichannel cathode ray oscillograph phonocardiograph was described to study the diastolic murmurs of rheumatic carditis (167). The incidence of extracardiac sounds in the dog and the effect of different variables on them was explored (168). In dogs and humans it was found that the first heart sound was significantly delayed in the absence of atrial systole or in the presence of an ectopic ventricular systole (169, 170). In the presence of an atrial pressure wave the authors chose the point at which ventricular pressure started to exceed the pressure level in the gradient established by atrial contraction as the onset of ventricular contraction. This finding supported the view that normally the A-V^2 valves are closed or nearly so before the onset of ventricular systole and that in ectopic ventricular beats the A-V valves are closed from an open position by atrial contraction. While this may be true, the reviewer believes that the onset of right ventricular contraction was obscured by the presence of a normal atrial pressure wave and that therefore the interpretation of the observations are open to question.

Ballistocardiography.—The value of the BCG^2 as an indicator of normal physiological events or as a diagnostic aid remains uncertain. Published rec-

ommendations for terminology and conventions would seem premature since there is no agreement as to what the essential requirements of a BCG are and what it is supposed to record (171, 172). The necessary instrumental frequency, together with adequate mechanical and electrical filtering to remove body impulse distortion, has not yet been fully ascertained (173, 174), and hence the form of the BCG depends upon the type of device used (175). Developments included an acceleration (176), a torsion (177), and an aperiodic BCG (178), together with improved recording by a microscope (179), and an asymmetrical shutter (180). In cadavers in simulated systole Starr *et al.* (181, 182) found that the BCG amplitude did not correlate well with cardiac output but, when corrected for body size, its amplitude was used to estimate the strength of cardiac contraction in relative terms. Reports of BCG used to indicate normal variables included typical patterns in young soldiers (183), in athletes (184), time relations between BCG movements and hemodynamic events (185, 186), values for velocity of body displacement and of body momentum (187), respiratory variations (188), comparative effects of cardiac glycosides (including gitalin) on the ECG and BCG (189), and cardiac drug evaluation in the dog (190). In patients with heart disease with high cardiac outputs Masini & Rossi (191) found that the velocity of body displacement was higher than in normal subjects. BCG changes in exercise (192) and after cigarette smoking (193, 194, 195) were used to separate those with coronary artery disease and as a prognostic aid in post-infarction follow-up (196). Essentially normal BCG were found in acute rheumatic fever (197) and aortic stenosis (198).

Kinetocardiography and electrokymography.—Various motions of the anterior chest wall during the cardiac cycle were studied in normal subjects (199 to 202). The significance of such measurements is not known to the reviewer. An automatic calibrator for EKY[2] cardiac densograms was described for use in determining cardiac output (203). Movements of the right atrial border observed with the EKY in human subjects were related to changes in shape rather than to changes in atrial volume (204). The value of the left atrial EKY as a diagnostic aid was considered (205, 206).

Heart contour and volume.—Grant (207) considered the significance of the functional flow pathways in the normal and diseased heart. A method by Rushmer *et al.* (208, 209) for studying the functional anatomy of ventricular contraction by measuring impedance between multiple pairs of intracardiac pin electrodes in the endocardium and epicardium of the ventricles of unanesthetized dogs was abandoned and replaced by the use of variable inductance gauges installed within the left ventricular chamber. Using the latter device, diameter changes were found by the same author (210, 211) to be of greater importance in blood ejection than shortening along the long axis of the heart. During anesthesia and thoracotomy, the cardiac silhouette and left ventricular size were reduced, followed by re-expansion of heart postoperatively. During treadmill exercise stroke volume increase was attained by more complete ejection rather than by increased diastolic dis-

tention and after exercise both systolic and diastolic diameters increased. The value of these measurements depends upon how accurately change in diameter at two intraventricular points reflects intraventricular volume. The observation that the hearts of normal and marathon runners are smaller after strenuous exercise is at variance with the preceding (212).

Normal coronary circulation.—Morphological studies were concerned with early human embryos (213), cardiac innervation (214), injection techniques for outlining the coronary architecture (215), blood supply of the sinoatrial node (216) and individual muscle bundles (217), cardiac vein drainage (218), and microscopical anatomy of myocardial vessels (219).

It is well to know that the coronary sinus pressure pattern in humans is related to the depth of catheter since deep catheterization can be particularly dangerous (220). Goodale & Hackel (221) combined the two techniques of saturation and desaturation to save time in measuring blood flow through the coronary sinus in man and dog by the nitrous oxide method. Waser & Hunzinger (222) used small secondary and delayed activity peaks occurring over the heart following intravenous injection of Na^{24} as an index of coronary volume flow relative to cardiac output, the latter being represented by large and early activity peaks. These experiments were complicated by the random activity of the surrounding noncardiac tissue, the smallness of the so-called coronary activity peaks, and lack of experimental proof that the latter represented indicator flow from the coronary system. Paul *et al.* (223) were able to quantitate separately the coronary flow effects of extravascular support and of active changes in smooth muscle of the coronary vessels.

Reports continued on the effect of various physiological states and of drugs on coronary flow. By use of a cardioscope inserted into the left atrium of dog and man dark blood was observed coming from the atrial wall and interpreted as direct proof of Thebesian drainage (224). Since left coronary volume flow is maximal during diastole when perfusion pressure is minimal, coronary inflow in the dog was increased significantly by lengthening the inflow circuit so that maximum coronary perfusion pressure occurred during diastole and minimum perfusion pressure during systole (225). By use of rotameters in dogs, no evidence was found of reflex control of coronary flow during ice water immersion (226). The relative contribution of ventricular compression and coronary resistance to phasic coronary sinus flow was assessed by Wiggers (227) in a variety of dynamic states, with the general finding that the net effect of ventricular compression was not to throttle coronary flow but to improve it. This is a revival of the supposedly discredited massaging theory. These results are at variance with those of Paul *et al.* (223) who found that, following abrupt reduction of extravascular support by experimental induction of asystole or ventricular fibrillation, coronary inflow under a constant perfusion pressure almost always rose significantly. Using rotameters Winbury *et al.* (228) found ATP to be the most potent dilator of the adenine-adenosinetriphosphate series. Using a mechanical stromuhr with constant perfusion pressure, Schofield & Walker (229)

observed coronary flow effects of a number of drugs and of vagal section and stimulation essentially similar to those of previous investigators. In the heart-lung preparation the coronary dilator effect of "soluble Khellin-Nokhel" was only 10 per cent of that of Khellin (230); in a similar preparation, addition of albumin to the perfusate increased coronary flow (231). In the isolated perfused rabbit and dog heart, a commercial muscle extract was found to have a coronary dilator effect similar to that of ATP (232). Crumpton *et al.* (233) reported that hexamethonium in the normotensive and renal hypertensive dog had little effect on coronary flow measured by the nitrous oxide method.

Coronary artery disease.—Reviews (234, 235) and an excellent monograph (236) have largely covered the field of the experimental problem of atherosclerosis. Coronary artery lesions were produced in the Cebus monkey and in rats by synthetic diets (237, 238, 239); in combination with renal hypertension, the number of lesions was doubled (238).

In humans with coronary atherosclerosis, studies covered various parameters including a chemical test, anatomical findings, relation to other conditions, and changes with treatment. Horlick (240) suggested a chemical test to separate the disease state from the normal based on the observation that the former showed an early onset and a high final level of turbidity in serum to which a lecithinase had been added. The incidence of intimal hemorrhage was found (241) to be much greater than that previously indicated by Wartman. It was demonstrated that the human atherosclerotic senile heart had a lower mast cell count than the nonatherosclerotic young adult or senile heart (242). The importance of very hot weather as a precipitating or predisposing factor in acute myocardial infarction was stressed (243). Progressive coronary artery atherosclerosis in humans was not a necessary concomitant of increased blood cholesterol levels in the hypothyroid state (244). The question of a causal relation between hypertension and coronary artery disease continued to be explored with the observation that hypertension did not seem to be a factor in producing coronary disease and occlusion among white men but was a definite factor in its causation among women and negroes (245, 246, 247). The common coexistence of ischemic heart disease and peripheral occlusive vascular disease was stressed (248). In patients with coronary artery disease, alimentary lipemia was increased and intravenous heparin accelerated plasma clearing (249). Weight reduction from caloric restriction and administration of ethinyl estradiol decreased lipoprotein and cholesterol levels (250, 251). Ovariectomy, estrogen therapy, and breast cancer reduced the incidence and severity of coronary atherosclerosis (252, 253). Ethyl chloride spray was regarded as effective for relief of the somatic component of cardiac pain (254). Heparin had no advantage over placebos in the therapy of angina pectoris or in effecting serum lipoprotein levels (255, 256, 257). Opinion was about equally divided as to whether anticoagulant therapy lessened the incidence of thromboembolic phenomenon and the mortality rate (258 to 263). The observation that after myocardial infarction blood

coagulability increased (except for the second to ninth day) for weeks to months might be pertinent here (264).

Coronary artery occlusion.—In vivo angiographies were reported for the dog heart before and after coronary artery ligation and for the human heart (265, 266). Following acute myocardial infarction in the dog and human, there was a decrease in cardiac output, circulation time, arterial blood pressure, and an increase in right and left ventricular end diastolic pressures, right atrial pressure, central venous pressure, and total peripheral resistance, to be followed later by a rising cardiac output and arterial pressure (267 to 270). This confirms previous observations of Freis in humans. As measured by right atrial and arterial pressure response, experimental dogs with chronic left myocardial infarction were comparable to normal dogs in their ability to tolerate prolonged acute hemorrhagic hypotension and resuscitation by intra-arterial or intravenous reinfusion of blood (271). The importance of an exercise test in evaluating heart disease was stressed by Eliasch *et al.* (272). In asymptomatic patients with healed myocardial infarctions, response of cardiac output, circulation time, and systemic blood pressure to exercise stress was the same as the response of normal individuals (273). This provides no support for the view that marked activity restriction is physiologically necessary in patients of this type. The experiments of Donald & Essex (274, 275) are pertinent here in showing that, following massive destruction of right heart muscle by vinyl acetate injection into its coronary artery supply, the surviving dogs developed good tolerance to treadmill exercise. The cause of the ability of the badly-damaged right ventricle to maintain an adequate cardiac output in rest and exercise is believed to reside in collateral development and in hypertrophy of the remnants of viable muscle.

Medical and surgical attempts continued to improve the blood supply to a myocardium whose natural blood supply had been reduced or removed. ACTH and cortisone prophylactically or therapeutically administered had no effect on the vascularity or rate of healing of experimentally induced cardiac infarction in the dog, and their use did not influence the immediate mortality following sudden coronary occlusion (276, 277). Cardiopexy was tried as a means to aid revascularization of infarcted areas (278, 279). Bloomer *et al.* (280) investigated the value to the heart of the many anastomatic connections between the coronary arteries and bronchial arteries which developed following pulmonary artery ligation. The value of the procedures of implanting the open end of an internal mammary artery in infarcted zones of myocardium and of creating artificial Thebesian channels was not established (281, 282, 283). A favorable appraisal of the value of the procedure would be possible if it were demonstrated that coronary sinus flow was significantly reduced after acute ligation of the implanted artery. The chronic effects of the aorta-coronary sinus anastomosis of Beck in dogs were evaluated by measuring retrograde flow in an acutely occluded left coronary artery branch at varying times after establishment of the shunt (284, 285, 286). The graft perfused the capillary bed of the acutely occluded coronary artery for

about five weeks postoperatively and then lost its functional contact with the capillary bed, probably because of obliterative venous changes. Simultaneously, intercoronary collateral vessels (increased retrograde coronary artery flow in the presence of clamped shunt) developed and persisted for at least a year. Thus, in dogs the Beck operation increased retrograde capillary flow early and intercoronary anastomoses later. These observations obviously apply only to the normal coronary circulation. Coronary sinus arterialization following coronary disease or occlusion could well have a quite different effect.

Cardiac input and output: methodology.—This is one of the most important measurements of cardiac activity for it, together with the proper pressure, gives insight into the state of performance of the heart. Methods of flow measurement were reviewed and classified (287). A modification of the old Volkman-Ludwig mechanical stromuhr was described (288). Rodbard *et al.* (289) employed a technique for the measurement of total cardiac input with rotameters in the open chest dog by shunting, pumping, and measuring all vena cava flow through a pulmonary artery branch and by measuring all coronary venous return in the other pulmonary artery. It has been the reviewer's experience that preparations with this degree of surgical insult without large infusions have a low cardiac output and cardiac work, and rapidly deteriorate. Electronic versions of Chauveau's hemodrometer of a hundred years ago were used by Scher *et al.* (290) to measure phasic blood flow in acute experiments and in the abdominal aorta of dogs postoperatively. The Potter electroturbinometer was used by Sarnoff & Berglund (291) to measure aortic flow in the dog. Although as currently used, this device has a rather large pressure drop, it should be useful and dependable in the same field as the rotameter and possibly in a wider field including the closed chest dog (292). Phasic venous flow was recorded in the open chest dog by an improved "stream bristle" flowmeter (293) and by a Pitôt type differential meter passed as a catheter into the superior vena cava of the closed chest dog (318). An electronic flowmeter system (still somewhat in the model stage as far as blood flow is concerned) appeared in which velocity was determined by the phase difference between an upstream and downstream ultrasonic wave (294). The pulse pressure method was applied to the quantitation of stroke volume in humans (295). To obtain a factor relating pressure to volume the cardiac output was determined initially for each subject by an independent method. It is not believed by the reviewer that the method as used has sufficient accuracy for human use. There is every likelihood that the pressure-volume relationship in the human arterial tree changes very quickly and largely during an experimental procedure, since it is known that in the dog deviations in cardiac output between the pulse pressure and control method of the order of 30 to 40 per cent can spontaneously occur (296). Starr *et al.* (297, 298) recommended a rough method of estimating stroke volume from a combination of pulse pressure, diastolic pressure, and age which could be performed "by any doctor with the apparatus he now has."

Attempts continued to substitute *para*-aminohippurate for oxygen in the application of the Fick principle (299, 300, 301). Sirota & Gordon (302) were unsuccessful in applying the method to measure regional contributions to cardiac output because of incomplete mixing in the great veins. Visscher & Johnson (303) stressed the existence and magnitude of potential errors in the conventional application of the direct Fick principle with special emphasis on the effects of cardiac and respiratory cyclic changes in either the oxygen concentration difference or the blood flow rate. The difficulty was illustrated practically by Nahas *et al.* (304) in which the direct Fick was compared with the dye dilution method during hypoxia. The dye dilution technique continued to grow in extent of use, and a number of papers should be read by those contemplating use of this technique (305, 306, 307). An improved dye injection pipette was described (308). An improved recording cuvette densitometer for cardiac output determinations by the dye dilution method was developed (309, 310). Injection of a mixture of Evans blue dye and P^{32} solution into the right ventricle of the anesthetized dog gave almost identical cardiac output values (311). In humans, comparisons continued to be made between the cardiac output determined by the Fick and dye dilution methods in the resting or anesthetized state with (as stated by the authors) good agreement (312, 313, 314). Dog experiments with P^{32} and T1824 pointed up the effect of successive cardiac output determinations on cardiac output through excessive blood loss (315). The limitations of the continuous infusion method for cardiac output were reinvestigated (316).

Right heart.—Variations in venous return were studied under a variety of conditions. Observations with the bristle flowmeter indicated that the heart plays an active role in insuring its own venous return (317). The greatest volume flow occurred during ventricular diastole at slow heart rates; with tachycardia 80 per cent of atrial inflow occurred during ventricular systole. In the closed chest dog with the Pitôt tube intermittent positive-negative pressure respiration increased superior vena cava flow significantly over that existing during intermittent positive pressure respiration (318). Active changes in postarteriolar tone (presumably veins) were demonstrated (319). Increased intracranial pressure augmented pressure and flow (rotameter) in both vena cavae, and it was suggested that such compression released a substance into blood similar to *l*-epinephrine or *l*-norepinephrine, which are known to produce the same hemodynamic effect (320).

The question of the regulation of the pulmonary circulation is still controversial. Dawes & Comroe (321) collaborated in an excellent review. The cooling effect of inspiration of cool air upon blood in the pulmonary circulation was small, a temperature difference of only 0.03°C. being recorded (322) between the pulmonary artery and left atrium for an air temperature shift from 20°C. to −18°C. In addition to the concepts of arteriolar tone and passivity, stress was laid on the role of the bronchomotor apparatus and its tone as an important factor in regulation of pulmonary hemodynamics (323). Stretch receptors were identified in the right and left atria responding to

changes in atrial filling (324, 325). Inflatable cuffs and special catheters with a balloon tip were developed for testing the physiological effects of pulmonary artery or bronchial occlusion (326 to 329). Contrary to popular belief, complete sudden occlusion of a main pulmonary artery in unanesthetized patients was well tolerated, did not produce shock or changes in the ECG. In the presence of a competent left ventricle this most appropriate hemodynamic compensation was attained in the normal subject without any marked increase in pulmonary artery pressure or change in cardiac output and in the presence of a high cardiac output of eight to ten times normal in the conditions of exercise and hyperthyroidism (328, 330). In normal subjects a significant relation was found to exist between pulmonary artery pressure and pulmonary arteriolar resistance (331). Whitaker (332) related the pulmonary hypertension in congestive failure complicating chronic lung disease to anoxia. McGregor *et al.* (333) demonstrated in mitral stenosis that pure oxygen breathing decreased pulmonary artery pressure and pulmonary bed resistance. Hypoxia in the normal, trained nonnarcotized dog immediately increased pulmonary artery pressure, heart rate, and cardiac output (dye) without change in left atrial pressure but the increased cardiac output could account for increased pulmonary artery pressure without postulating increased pulmonary vascular resistance (334). In dogs unilateral hypoxia was observed (335) to reduce considerably the calculated pulmonary blood flow in the hypoxic lobes. However, acute atelectasis did not reduce the calculated blood flow through the exposed atelectatic human lung (336). Hypercapnia was implicated as a heavily contributing factor in producing pulmonary hypertension in patients with pulmonary emphysema and fibrosis for recovery followed mechanical ventilation (337). Comroe *et al.* (338) were able to elicit profound reflex cardiopulmonary changes in the chlorolosed cat with serotonin injection. Geoghegan & Lam (339) studied the effects of left heart embolization. In experimental vena cava air embolism there was an advantage to survival rate of left side down versus supine or right side down position, the benefit coming from removal of air or its trapping in the right ventricle out of the blood stream for ultimate slow release (340, 341). Acute pulmonary embolization with lycopodium spore injection increased pulmonary artery pressure, cardiac output, and cardiac work, but did not affect left ventricular oxygen usage or coronary sinus flow (342). Severe pulmonary embolization with intravenous lycopodium spores, air, or anaphylactic shock caused necrosis and fibrosis of the right ventricle (343). Trypsin in almost any dose (in dogs) had no effect on pulmonary embolism after its production but its infusion before and after embolization usually prevented its persistence (344). Ganglionic blocking agents in experimental (pumice stone) pulmonary emboli were found to be ineffective (345).

Wiggers (346) wrote a critical review of the value of pressures recorded from a catheter wedged into a peripheral branch of the pulmonary artery, and Burton (347) regarded these measurements as unsound. Comparison of wedged pulmonary artery catheter pressure was made with directly meas-

ured left atrial pressure in human subjects by entering the latter cavity through an atrial septal defect or by needle through a thoracotomy (348, 349) or by needling the closed chest directly (348, 350 to 353) or indirectly through esophageal bronchoscopy (354). Variations in the pulmonary artery pulse did not influence the shape or mean value of the wedged pressure curve (355). While the pulmonary artery wedged pressure curve was not always similar in pattern to the left atrial pressure curve, the mean pressure agreement of the two measurements was generally good in the normal and a number of abnormal states (356). These investigations overcame some of the hazards and technical difficulties of recording from the left atrium and indicated that this is a valid physiological measurement reflecting pressure changes in the left atrium.

Miscellaneous reports are those of multiple pulmonary lesions in explosive decompression (357), chronic massive thrombosis of the pulmonary arteries (358), and characterization of the right atrial pressure pattern associated with tricuspid regurgitation and pulmonic stenosis (359, 360).

Left heart.—The physiology of cardiac output was considered by a number of investigators. The determinants of cardiac output were discussed (361). The oxygen content of arterial blood was advanced as the primary factor in the regulation of cardiac output in the intact animal. This was based on the experimental finding that acute isovolemic anemia in anesthetized dogs increased cardiac output without increasing right atrial pressure; with restoration of a normal hematocrit, cardiac output returned to normal without change in right atrial pressure (362). Observations were made on the cardiac output (or cardiac work) response of the heart to mild exercise. This is important because it may ultimately permit classification of hearts on the basis of maximum cardiac work response. Following moderate treadmill exercise cardiac output was observed to be approximately doubled in humans and increased about three times normal in the dog (363, 364). These values probably do not approach the maximum for the left heart. Using the recording densitometer, the reviewer found in normal subjects at sea level and in the native Indians of Peru at a three-mile altitude cardiac output values as high as 35 to 40 liters/min. during strenuous treadmill exercise (unpublished observations).

Cardiac output was unchanged with cyclopropane anesthesia (365) and increased with thiopental (366) and ether anesthesia (367). The danger of ether was stressed in patients in whom reflex release of *l*-epinephrine or *l*-norepinephrine was absent, for the usual increased cardiac output obtained with ether at a surgical plane of anesthesia was converted to a decreased cardiac output in acutely adrenalectomized dogs (368). The effect of variation in venous return was observed by the use of leg tourniquets which reduced cardiac output (369) and by the use of the arm chair position in which cardiac output was considerably less than in the recumbent position (370).

The effect of drugs and various clinical states on cardiac output was observed. As judged by the pulse pressure method in dogs, reserpine and chlor-

promazine decreased cardiac output (371, 372) and *l*-epinephrine and *l*-arterenol had similar effects on cardiac index and stroke index (373). In the reviewer's opinion the adequacy of the pulse pressure method has not been sufficiently established to warrant its use with various drugs which may in themselves change the pressure-volume relations in the cardiovacular system. Hexamethonium and amobarbital (Amytal) were used to artificially reduce the heart's effort (374). Cardiac output (by the acetylene method) did not rise in paraplegics with bladder distention (375). Aortic flow was increased and peripheral resistance decreased in patients with Laennec's cirrhosis, and paracentesis in such patients with tense ascites increased the cardiac output (376, 377). The output of the heart was often quite high in active and extensive Paget's disease as a result of increased bone vascularity and without evidence for arteriovenous shunts (378, 379). Aortic flow was measured in hemorrhagic fever (380) and was decreased in the hepatectomized dog (381). Active rheumatic fever apparently impairs the functional efficiency of the myocardium, for supine bicycle exercise did not effect the cardiac output in children with acute rheumatic carditis, but did increase it to high levels (18 to 27 l./min.) in those who had recovered (382).

The effects of mitral valve disease have attracted considerable investigative work. Esophageal pressure pulse patterns were recorded in the normal subject and in mitral insufficiency (383). The hemodynamic and endocrine responses to experimental mitral stenosis were investigated (384). Theoretical considerations of Rodrigo (386) indicated the formula of Gorlin & Gorlin to be somewhat better than that of Silber for estimating valve resistance. The fundamental hemodynamic alterations in patients with mitral stenosis at rest (387) and with the Valsalva maneuver with and without autonomic blockade continued to be investigated (388, 389, 390). The demonstration that lanatoside C in patients with rheumatic fever and mitral stenosis increased cardiac output, cardiac work, right ventricular pressure, and systolic blood pressure is evidence to support its early use (391). Lung biopsy in this condition does not necessarily predict the degree of benefit from valvulotomy for, although increased interstitial tissue and thickening of alveolar and pulmonary arteriolar walls were observed, patients were generally greatly benefited by commissurotomy (392, 393, 394). The existing impairment of pulmonary oxygen diffusion capacity (393, 395 to 397) was little affected by operation, but the increase in percentage of venous admixture in mitral stenosis was largely corrected (395). Hemodynamic factors showed the most marked improvement with decrease in pressure in the pulmonary circulation, increased cardiac output, decreased heart size, improvement in functional capacity, and better exercise tolerance (396a, 397a, 398, 399). The chief complication appeared to be a reactivation of an acute rheumatic state (397a, 400, 401, 402). The effect of severe mitral stenosis on body composition was studied before and after valvuloplasty. Immediate postoperative changes in fluid and electrolytes were on the same nature but greater in degree than those seen in noncardiac patients after severe operative

trauma. These changes were increased nitrogen and potassium excretion and fluid retention in the presence of positive sodium balance and decreased serum sodium and increased serum potassium (403).

The dynamics of aortic valvular disease in rest and in exercise were described by Goldberg *et al.* (404) and physiological observations made by Gorlin *et al.* (405). Following surgical correction of severe aortic insufficiency by a valvular prothesis, cardiac output and stroke volume increased and mean circulation time decreased (406, 407).

The effect of tetraethylammonium bromide on acute pulmonary edema was indicated (408). Factors effecting epinephrine pulmonary edema in rats were investigated (409). Attention was called to the possible role of a "throttle valve" action of the pulmonary veins in acute pulmonary edema syncope (410). In patients with pulmonary congestion and edema, arterial oxygen saturation was found to be generally greater than 93 per cent in the presence of widespread râles (411).

Contractility.—Studies continued in this difficult field using isolated portions of myocardium. Diastolic shortening of isolated myocardial strips decreased the amplitude of systolic contraction (412). Summation of contraction and incomplete tetanus consistently occurred in frog ventricular strips following elevation of bath temperature (413). The more favorable situation in ventricular muscle during the staircase phenomenon was related to a reduction of internal ion content (postassium or sodium) rather than to a change in internal ion concentration. Contracture was found to be induced by excessive decrease in internal ion content, while digitalis and related substances acted by blocking re-entry of potassium into the cell, thereby decreasing internal ion content (414). Maximum work of stretched left atrial strips from the dog was determined and calculated as equivalent to a left atrial luminal pressure of 150 mm. water (415). A number of agents were found to potentiate the ionotropic response of isolated papillary muscle to *l*-epineprhine (416). Identical effects were obtained by *l*-epinephrine and *l*-norepinephrine on force of contraction and speed of action of the cat's papillary muscle (417).

The problem of estimation of the state of performance of the whole heart is more difficult and has been approached by measuring the force required to move the ends of a strain gauge arch attached to the myocardium (418) and by relating atrial or ventricular end diastolic pressure to stroke work during acute ventricular loading with infusion or exercise. Using the resistance strain gauge arch, change in heart rate and in heart size by intra-arterial transfusion had only minimal effects on heart contractile force, while accelerator nerve stimulation, arterenol injection, and increased initial length of the muscle segment between the two points of attachment of the strain gauge arch gave substantial increments in contractile force (419, 420). In studies at rest and during exercise on patients with cardiovascular lesions affecting primarily the left ventricle, it was observed that those with normal pulmonary capillary pressure (regarded as an index of left ventricular diastolic pres-

sure) and normal pulmonary artery pressure showed good correlation between the increase in pulmonary capillary pressure and stroke work (421). In using the Potter turbinometer for cardiac output and the rotameter for coronary flow, Sarnoff & Berglund (422) reported that during ventricular loading by infusion a similar relationship occurred between atrial pressure and stroke work in the presence of *l*-epinephrine effect, coronary artery constriction, severe anemia, and aortic constriction, each variable inducing a different pressure-work curve. In our own laboratory (423), in the open-chest and closed-chest dog with rapid blood infusion (increased venous return and blood volume), the data showed almost perfect directional correlation between left ventricular end diastolic pressure and stroke work; with moderate infusion rates in the closed chest dog there were exceptions; in the trained, unanesthetized dog immediately after treadmill exercise (increased venous return), directional changes in stroke work and left ventricular end diastolic pressure were not related (364). Thus, these studies showed gradation in the degree of directional correlation, the deviations being more marked as one more closely approximated the normal state. It is obvious that further work and more suitable techniques are necessary in order to obtain an accurate estimate of the performance of the normal heart. The reviewer does not know of any good reason why diastolic ventricular pressure should necessarily correlate with stroke work but, presumably, stroke work should correlate with tension in the ventricular wall which is related to both diastolic size and cavity pressure.

Changes in cardiac failure and miscellaneous heart disease.—Reviews appeared covering a portion of this field and were concerned with sodium excretion and water and electrolyte metabolism (425, 426).

Experimental cardiac failure was investigated in the isolated mammalian heart in which only the left ventricle performed work and exhibited volume change (427). Such experimental conditions as acapnia, altered or depleted substrate, and constant diastolic volume did not play a determining role in the mechanism of experimental failure which was characterized by a decline in mechanical efficiency with little or no impairment of energy liberation.

Experimental congestive heart failure was produced in rabbits by severe aortic constriction (428). In dogs in cardiac failure as the result of pulmonary stenosis and tricuspid insufficiency the concept of venous pressure elevation alone did not appear to be an adequate explanation of the markedly decreased sodium excretion (1 per cent of normal). Such excretion could vary independently of the venous pressure, and the authors felt that the defect in sodium excretion was predominantly tubular in origin (429).

In patients, anoxia from uncomplicated chronic lung disease rarely led to right heart failure, but failure was easily precipitated by marked reduction in arterial oxygen saturation (less than 80 per cent) from airway infection (430). Radiocardiograms with I^{131} albumin in patients in congestive heart failure showed a distinct widening between humps derived from the right and left hearts which could be related to cardiac dilation or reduced cardiac

output (431). Elevation of myocardial creatine values in heart failure were found to bear a relation to the degree of decompensation (432). The edema in skeletal muscle from congestive heart failure was characterized by an increase in both extra- and intracellular fluid, and sodium and chloride content, and its treatment led to a reversal of these shifts (433, 434). Long-term studies of sodium balance in patients with congestive heart disease suggested that a portion of the intracellular cation was not osmotically active (435). The effect of hypophamine (Pitressin) on fluid retention in congestive heart failure was studied by White *et al.* (436). Congestive heart failure did not affect the total urinary catechol excretion (437). Patients with congestive heart failure had a significantly lower excretion of thiamine after a loading dose than did normals, but with mercurial diuresis there was a significant increase in its excretion (438). During recovery from beriberi heart failure, a decrease in cellular osmolarity was shown (439). Red cell volume (P^{32}) and plasma volume (I^{131}) were both increased in congestive heart failure and fell with compensation (440). Fejfar & Brod (441) used adrenergic blocking agents to show that the tone of the arterial and venous systems was largely increased in congestive heart failure by nervous means. Similar effects were noted by Shuman *et al.* (442).

The development of myocardial lesions was studied in a number of states. In bilaterally nephrectomized dogs, lesions developed and hypertension accentuated them (443). A selective fibroblastic derangement was demonstrated in tissue cultures of the chick embryo heart after exposure to filtrates of beta-hemolytic streptococci or to filtrates from sera of patients with active and inactive rheumatic fever (444). Selective necrosis of cardiac (and skeletal) muscle was induced experimentally by injection of crystalline streptococcal proteinase and various crude proteolytic enzyme solutions, and the findings were discussed in relation to their possible implication for pathogenesis of cardiac lesions of rheumatic fever and other states (445, 446). The hemodynamic changes in the anemic human heart were reviewed (447), and the ability of the anemic dog to tolerate intra-arterial blood infusions was tested (448). Harvey *et al.* (449) found that myocardial insufficiency and hypervolemia were not only important causative agents in the circulatory dysfunction of the chronic constrictive pericarditis but were to some extent reversible.

Hypertrophy.—Grant (450) reviewed various aspects of cardiac hypertrophy. The interrelation of hormonal factors was particularly stressed in the development of cardiac hypertrophy in the rat. Heart-weight followed closely body-weight changes during normal growth or during starvation (120 to 240 gm.), but no correlation was found between heart weight (or left ventricle weight) and arterial pressure in normal growth, aortic narrowing, and hypophysectomy (451). Aortic constriction that caused in normal rats hypertension and cardiac hypertrophy had no such effect in hypophysectomized rats, but subsequent therapy with growth hormone or lyophilized anterior pituitary restored hypertension and cardiac hypertrophy (452, 453).

However, if therapy was carried out in this situation with adrenocortical hormones the cardiotrophic effect of somatotrophic hormone was inhibited (453, 454). Cardiac hypertrophy induced in rats by kidney removal or implantation of desoxycorticosterone acetate pellets in the presence of renal hypertension could be abolished by kidney or pellet removal, and hence the process was reversible (455). Severe carbon monoxide hypoxia in infant rats gave increased heart weight and vascularity lasting at least two months after return to normal air, but this hypertrophy had a deleterious effect on the rat's later ability to withstand stress (456).

Sustained hypotension.—A critical evaluation of the nature and treatment of shock has appeared (457). Physiological studies were concerned with the response of hypotension associated with hemorrhage to transfusion and drugs. Myocardial failure arising in late hemorrhagic hypotension in the dog was ascribed to insufficient coronary flow (458), since the left atrial pressure rose while the stroke work fell, and the process was reversed by increasing left coronary inflow but not by intra-arterial or intravenous transfusion. In similar experiments in the reviewer's laboratory elevation of left atrial pressure or end diastolic pressure indicative of left ventricular failure was not observed. Various differences in experimental technique might explain the conflict, such as the fact that in the Sarnoff preparation blood could flow into the animal from the arterial reservoir during the hypotensive period thus causing increased loading of the left ventricle and increased left atrial pressure (459).

The response of the heart to intra-arterial and intravenous transfusion in the treatment of experimental hemorrhagic hypotension was considered in a symposium (459) and elsewhere (460). There was general experimental agreement that the response of cardiac output, systemic arterial pressure and left coronary inflow during reinfusion, was immediately adequate and of the same order of magnitude to both routes of transfusion with the possible exception of hearts in which there was an extreme bradycardia and a negligible arterial pressure or in those hearts which were essentially in asystole. In the latter situation there was the suggestion that intra-arterial transfusion was transiently somewhat better. Possibly this area should be explored further for differences in response to the two routes of transfusion. There were no significant changes from normal levels of ATP during the periods of decreased blood pressure.

Early in experimental hemorrhagic hypotension, *l*-norepinephrine increased cardiac output and systolic blood pressure, but later, after appearance of irreversible shock, it had no effect on these parameters (461). The peripheral vascular and cardiogenic actions of metaraminol bitartrate (Aramine) were separately stressed. In normal subjects its peripheral action was indicated by a decrease in heart rate and an increase in systemic systolic and diastolic pressure, pulmonary artery pressure, peripheral resistance, and cardiac work in the presence of a normal cardiac output (462). However, in experimental "cardiogenic shock" from hemorrhagic hypotension or de-

creased coronary artery inflow, its cardiogenic action was shown (463) in the augmentation of cardiac output, systemic blood pressure, coronary flow, and stroke work at an equivalent filling or atrial pressure.

The value of infusions and drugs in the treatment of shock associated with myocardial infarction continued to be explored. Intra-arterial and intravenous transfusions in dogs were equally effective in a state of acute hemorrhagic hypotension superimposed on chronic left myocardial infarction (271). Cahn *et al.* (464) advocated treatment by a combination of an anesthetic "cocktail" and hypothermia. Of the sympathomimetic drugs, *l*-norpinephrine was considered a valuable therapeutic adjunct (465 to 470). In patients with low venous pressure phenylephrine (Neosynephrine) was effective (471). That *l*-norepinephrine produced substantial increments in heart contractile force in addition to its recognized pressure effects in the dog was supportive evidence of its value (470).

Hypothermia.—This is an expanding field of interest. Studies were concerned with changes in myocardial function in severe generalized hypothermia. Resumption of heart beat in the early rabbit embryo in tissue culture occurred after exposure to −10°C. and occasionally after exposure to −75°C. (472). Additional observations included the following: marked reduction in heart rate and prolongation of systole and isometric relaxation, the latter occupying most of diastole (473); prolonged depression of arterial pH (474); reduced coronary peripheral resistance (475); decreased coronary flow and cardiac oxygen usage (476); increased heart contractile force and reduced ionotropic and pressor responses to drugs (477); maintenance of systemic arterial pressure in the absence of anesthesia (478); and decreased blood volume (479) and serum potassium (480). Ventricular irritability and incidence of fibrillation were high even with focal cooling (481) and were generally not amenable to massage and counter shock (482). However, the situation was greatly improved by the intracoronary injection of neostigmine (Prostigmine) (483) or potassium chloride (484) with subsequent massage and counter shock. Reference to clinical use of this situation will be found in the next section of this chapter.

Surgical approaches of physiological interest.—Some of the procedures and approaches which have greater usefulness in the surgical field or those which are of value in physiology but have not yet been used in physiological problems are included here. These tools should be of considerable interest to the physiologist.

Cardioscopes were used to visualize intracardiac structures (224a, 485). Digital exploration of a myocardial chamber through a rubber diverticulum sewed to the atrial or ventricular wall was reported by Gross *et al.* (486) in humans and Glenn in dogs (487).

Homotransplantation of the dog heart and of the heart-lung (under hypothermia) was attempted with survival periods ranging from hours to weeks (488 to 491). Lack of cellular infiltration suggested a biochemical agent as the destructive medium. Experimental surgical methods for induction of

cardiac lesions included rupture of chordae tendinae by catheter for creation of chronic tricuspid insufficiency (492), chronic pulmonic stenosis by constricting bands or direct suture in the infundibular and conus regions (493 to 496), use of a plastic button for ventricular septal defect (497), septal resection for atrial defect (498), subclavian-pulmonary artery anastomosis for right to left shunt (499), and left atrial-inferior vena cava anastomosis for right to left shunt (500). Surgical methods included corrections for the following: atrial septal defect by direct suture, attachment of plastic button or sheeting, atrioseptopexy, invagination and suturing of a pericardial (or plastic) pocket to atrial wall defect (501 to 506); tricuspid stenosis and aortic stenosis by commissurotomy (507, 508, 509); mitral insufficiency by direct suture (510), or plastic ball prothesis (511); aorticopulmonary fistula by division and suture (512); and aortic insufficiency by plastic ball prosthesis (406). Indications for surgical correction of interatrial defect or for pulmonary resection in man were tested by temporary occlusion of the defect (513) or of a pulmonary artery (328, 330).

Oxygenator-pump systems for partial or total bypass of the heart and lungs were described (514 to 517), and these were supplemented by Glenn & Sewell (518) with a coronary sinus pump and ventricular fibrillation to give a dry field and to prevent air embolism. Induction of operative approaches that permitted a period of circulatory reduction or stoppage compatible with intracardiac surgery under direct vision was stressed by Swan & Zeavin (519). An excellent monograph appeared on this subject by Senning (520). Differential cardiac hypothermia (521) and general hypothermia alone or with clamping of large vessels was used to obtain a dry field and to lower cardiac metabolic rate (522). These procedures were generally effective as evidenced by reports of 15 consecutive survivals in the open-chest hypothermic dog after prolonged bypass of heart and lungs by means of a pump-oxygenator (523) and of survival as the rule in the closed-chest hypothermic dog in the presence of prolonged ventricular fibrillation and a small intermittent extracorporeal flow (524).

The problem of cardiac arrest and ventricular fibrillation was approached from a number of angles. Vanremoortere & Dalem (525) measured the necessary defibrillatory current and impedance of the heart in electrical counter shock, and a new electronic cardiac defibrillator and pacemaker was described by McCombs, Herrod & Mackay (526). Wégria *et al.* (527) gave a resumé of the usefulness and limitations of electrical countershock, cardiac massage, and drugs in cardiac resuscitation from ventricular fibrillation. The acute and chronic effects of electrode application and massage on cardiac muscle were determined by Thoma (528) and Tedeschi & White (529).

Congenital heart disease.—There were four fatalities in 5700 right heart catheterizations in eight medical research units (530). From determinations of percentage saturation in the hand and foot of newborn infants the ductus arteriosus was found to be either functionally or anatomically closed within the first three days of life (531). Of various congenital malformations in patients indigenous to high altitude, patent ductus arteriosus and persistent

interatrial communications were more prevalent that in those at sea level, and the lower oxygen tension was presumed to have the decisive influence (532). Morse & Cassels (533) were unable to confirm previous work that basal oxygen consumption is lower in patients with marked arterial unsaturation.

The adaptative mechanisms in cardiorespiratory function in patients with cyanotic heart disease were reviewed (534). Cyclic variation in oxygen saturation of blood in the pulmonary artery was demonstrated in patients with patent ductus and pulmonary hypertension, and on this basis systolic rate of left to right flow through the ductus was found to be greater than the diastolic flow (535). By varying the oxygen content of inspired air in such patients, Burchell *et al.* (536) were able to produce differential effects on the pulmonary and systemic artery pressure and to initiate, increase, decrease, or reverse the shunt flow. Distinctive patterns of the dye dilution curve were obtained associated with cyanotic and acyanotic heart disease and used to indicate the volume of shunted blood. In the cyanotic group, this fraction appeared as an abnormal hump on the build-up slope of the curve representing dye which had bypassed the pulmonary circuit through the intracardiac defect as a right to left shunt (537). In acyanotic heart disease, dye dilution patterns were characterized by a prolonged disappearance slope and relative reduction in peak caused by the left to right shunt (538).

Since it is possible to reverse shunts by physiological expedients, the general association of elevation of pulmonary artery pressure with patencies of the atrial system, ventricular septum, and especially the ductus arteriosus was considered (539). In the presence of severe pulmonary hypertension, surgery was contraindicated with a functioning right to left shunt, since it could be caused by irreversible pathological changes in the coronary bed (540). Under some circumstances severe pulmonary hypertension was relieved by surgery (541).

Available space or late receipt has precluded consideration of a large number of additional contributions in all fields.

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METABOLIC ACTIVITIES OF THE KIDNEY[1,2]

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The title will be interpreted in a rather broad sense. Articles appearing during the past year dealing with the role of the kidney in the metabolism of various useful substances by the body are first reviewed. After that material on the intrinsic metabolism of the kidney will be taken up. The reviewer admits that decisions on what involves metabolism and what does not are sometimes arbitrary.

Production by the Kidneys of Compounds Metabolized by Other Tissues

In the classical sense this would be the type of process constituting the metabolic activities of the kidney. Processes of this type are ordinarily thought of as taking place in the liver. Gluconeogenesis and blood sugar regulation, ketone body formation, and plasma protein production are examples of such activities. In recent years considerable evidence has accumulated indicating that the kidney is capable of some of these functions. Boulanger (1) discusses hepatorenal biochemical relations. It has been fairly well established that the kidney can produce glucose from other compounds. Kleinschmidt (2) reviews recent work bearing on the role of the kidney in carbohydrate metabolism. He takes up the mechanisms involved in the excretion and reabsorption of glucose by the kidney and in addition reviews the work bearing on the formation of glucose by the kidney. New work in this field has been carried out by Teng (3) who has made a study of glycerol and pyruvate metabolism in rat kidney slices. He measured the disappearance of these from the medium and the change in lactate and glucose concentration in the medium. Both glycerol and pyruvate led to an increase in glucose production under aerobic conditions but not in the absence of oxygen. Lactate was formed both aerobically and anaerobically when pyruvate was the substrate but not when glycerol was the sole substrate. However, when glycerol was added with pyruvate there was a marked increase in lactate formation. The same author (4) has found that kidney slices from diabetic rats produced significantly greater amounts of glucose than do controls.

[1] This review covers the period from that of the last review on the Kidney (May 1, 1953) to approximately May 1, 1954.

[2] The following abbreviations are used in this review: ACTH (adrenocorticotropin); ADH (antidiuretic hormone); ADP (adenosinediphosphate); ATP (adenosinetriphosphate); CoA (coenzyme A); DOCA (desoxycorticosterone acetate); GFR (glomerular filtration rate); PAH (*p*-aminohippuric acid); RPF (renal plasma flow).

[3] The review was made possible (in part) by a research grant (A-52-C3) from the National Institutes of Health, Public Health Service.

Pyruvate was added substrate. He found that administration of insulin to the animal some time prior to sacrifice increased the uptake of glucose by the slices in both normals and diabetics. Presumably some insulin action was still operating after removal of the kidneys from the animal. One would have liked to see whether insulin would act directly on kidney slices as is the case with skeletal muscle. The finding that prior insulin administration reduces glucose production by the diabetic kidney is similar to that found for the liver. In the case of the diabetic liver it has been shown that direct addition of insulin to the tissue slice does not have this effect. The hormone must be given to the whole animal before sacrifice. This suggests that this effect of insulin may be secondary to a primary effect elsewhere. It would be interesting to see whether the same applies to the kidney. Chiquoine (5) studied the distribution of glucose-6-phosphatase in frozen sections of mouse kidney. The enzyme is found in the proximal convoluted tubule, concentrated at the basal pole of the cells, and in portions of the glomerulus. The author feels that this is an enzyme distinct from nonspecific acid and alkaline phosphatases. He suggests that this enzyme is connected with the production of glucose by the kidney. Bartley (6) has shown phosphopyruvate to be synthesized by washed kidney particles and finds a very high turnover rate for this compound. He suggests that the formation of this compound may be a key step in the resynthesis of glucose from C_4 and C_3 compounds.

Bracq *et al.* (7) examined the question of whether endogenous glucose in the blood is in a different physicochemical state than ordinary glucose in water solution. They tested this by injecting labeled glucose and determining the relative specific activities of glucose in blood and urine. The results indicated that the kidneys, in excreting this substance, make no distinction between exogenous and endogenous glucose. The authors conclude that if there is a physicochemical difference between these two it cannot be shown with their method. Miller (8) reports that insulin decreases the Tm of glucose in normal subjects. The effect, which is not too marked, should be examined further since it could give information as to the primary action of insulin in general. Miller & Bogdonoff (9) find that insulin effects an antidiuresis in subjects in whom diuresis is being produced by intravenous glucose or mannitol. Increased urinary concentration of electrolyte and of loading solute also occurs. No antidiuretic effect is manifested when insulin is given to subjects with water diuresis. Marsh & Miller (10) report glycogen synthesis by kidney slices. They find the optimum medium similar to that for the liver synthesis of glycogen and hence markedly different to that for muscle.

Some reports have appeared dealing with the kidney and fat metabolism. Svanborg (11) discusses the question of renal hyperlipemia. Geyer *et al.* (12) found that pyruvate decreased the octanoate metabolism of kidney slices and acetate decreased oxidation of octanoate to CO_2 when the medium was high in potassium. Another paper from this laboratory (13) reports the effects of inorganic ions on fatty acid metabolism of kidney slices measuring labeled CO_2 and acetoacetate production. Potassium or lithium was varied

at the expense of sodium. Potassium but not lithium causes an increase in octanoate metabolism by the kidney. Schwab & Lotspeich (14) studied the excretion of acetoacetate in the dog. The kidney treats this compound as a threshold substance—there is complete tubular reabsorption at low plasma levels. At high plasma levels tubular reabsorption stops. The authors suggest that the absorbed acetoacetate may serve as fuel for the tubule cells. Leninger & Greville (15) report that betahydroxybutryric acid is oxidized aerobically by suspensions of kidney particles (mitochondria).

Water Metabolism

The kidney regulates its water excretion not only for osmoregulation of the body fluids, but also for their volume regulation when the water content of the body is abnormal although solute and water concentrations are in their proper state.

Water excretion concerned with osmoregulation.—The subject of osmoregulation, both under water loading and water deprivation, has been actively investigated in recent years, and several reviews have appeared recently This subject has been summarized by Van Dyke (16). Kellogg *et al.* (17). have developed a technique for constant gastric administration of fluids in rats which they maintained for several hours. In this way they attained a steady state balance between input and excretion. Additional fluid administered as Ringer's solution was more rapidly excreted than when given as water. The upper limits of saline diuresis is three times that obtained with distilled water. This makes an interesting contrast to the findings in man.

Engstrom & Liebman (18) report on a case with a cerebral lesion obviously involving the osmoregulatory mechanism. This subject had polyuria and chronic hypernatremia and hyperchloremia. These latter disappeared when the polyuria was controlled by beta-hypophamine (Pitressin). After discontinuance of beta-hypophamine the hyperosmolar state promptly recurred, mainly through salt retention if cortisone were given and through water diuresis when cortisone was not given. Levkoff *et al.* (19) produced diabetes insipidus in dogs by hypothalamic puncture and studied the renal concentrating ability under osmotic loading (mannitol) when the animals were hydropenic. The animals showed a definite renal concentrating deficit; beta-hypophamine administration uniformly restored concentrating capacity to normal. The animals always showed some concentrating ability, and this improved with time. A reduction of daily water intake to one-half the amount drunk spontaneously when water was available *ad libitum* did not cause symptoms of dehydration. Dingman (20) studied five patients with polyuria, testing them with intravenous beta-hypophamine, nicotine, and hypertonic saline. All subjects responded to beta-hypophamine. Responses to the other agents were not consistent among these cases and suggests that diabetes insipidus can result from deficiencies in different parts of the osmoregulating mechanism. White *et al.* (21) find that patients with diabetes insipidus respond to intravenous hydration with 5 per cent glucose with an

immediate maximal diuresis, not showing the delay seen in normals. The authors discuss the possible physiologic basis for this.

Calcagno *et al.* (22) find that the premature infant cannot concentrate the urine as well as the adult in the hydropenic state, nor can it conserve sodium as well. On the other hand, the premature infant can excrete water as readily as the adult when sujected to water loading. Ames (23) studied in infants the diuretic response to water loading. No evidence of diuretic response was obtained during the first three days of life. After that capacity to respond with diuresis developed rapidly in premature as well as in full-term infants. Antidiuretic hormone was found in urines of infants under three days of age after fluid deprivation. These results indicate an interesting field of investigation that should be continued. They suggest the possibility that learning may play an important role in diuresis.

Water excretion concerned with volume regulation.—The mechanisms whereby the kidney regulates the fluid content of the body has puzzled physiologists for many years. It has long been known that when physiological saline is added to the body already in proper fluid balance, this extra volume will be eliminated by the kidney over the course of some hours. This process does not involve any osmotic adjustment, indeed it would occur if plasma were given. It is a correction of the volume of fluid in the body operating probably through an increase in blood volume which would share an increase in extracellular volume. This need for some such controlling mechanism was expressed by Peters (24) years ago, and he felt that there should be some process that could sense "the fulness of the blood stream which may provoke diuretic response on the part of the kidneys." It is surprising how frequently writers ascribe this control as being mediated through the osmoreceptors, although they never attempt to show how a volume factor can affect an osmoreceptor. Borst (25) promotes the hypothesis that increases in blood volume (i.e., intake of saline) increases cardiac output which in turn acts on the osmoreceptors like a decrease in electrolyte concentration in the plasma. Another theory for volume control of urine output consists largely of mechanical considerations based on heart-lung observations. This theory is reviewed by Borst (26) who cites several supporters to the view. Essentially it proposes that increase in blood volume increases cardiac output which in turn causes an increase in renal blood flow which results in an increase in urine volume—all assumptions yet to be established. Actually work appeared during the past year that might cast some doubt on their validity. Blackmore *et al.* (27) studied the effect of histamine on renal hemodynamics. The renal blood flow increased although the mean arterial pressure diminished. An antidiuretic effect was observed in all experiments. Handley & Moyer (28) report that an adrenergic blocking agent, Ilidar[4], may

[4] The chemical name of Ilidar is 6-allyl-6, 7-dihydro-5-dibenz [c, e] azepine hydrochloride.

reduce mean arterial pressure without altering renal plasma flow or kidney function. Another hypothesis that has been advaned is that there is a volume receptor within the cranium. Fishman (29) tried to find evidence for such receptors. He determined the effect of varying the intracranial venous pressure, venous volume, and the pressure and volume of the cerebrospinal fluid on renal function in the dog. He was able to produce no significant change in renal function, so that his experiments fail to support the concept of an intracranial volume receptor.

Gauer and his co-workers (30) have presented evidence for a regulating mechanism having its receptor areas in the walls of the intrathoracic portions of the venae cavae, the pulmonary veins, and the atria. Anatomical evidence of sense organs with nerve connections in these areas was described some years ago (31). Gauer and his group have proceeded on the working hypothesis that there are stretch receptors which initiate reflexes affecting urine volume. They increased the fullness of the intrathoracic vessels in dogs by subjecting them to negative pressure breathing and found that this resulted in a definite increase in urine volume. They cite an extensive array of other experimental conditions in which urine flow is correlated to the degree of filling of the intrathoracic vessels but not to degree of filling of veins in other areas. In a more recent paper (32) this group has reported their findings on the application of negative pressure breathing to human subjects. They found that this procedure produced definite increases in urine volume, without a change in urine pH, total urine sodium and potassium excretion, or in endogenous creatinine clearance.

These authors do not stress the operation of the opposite process—that is, a reduction of blood in the thoracic veins causing a reduction in volume of urine if there were already a diuresis produced by water loading. The possibility of such an action, however, seems to be implied in their papers, and it is not unlikely that it occurs. The situation may be complicated by the operation of reflexes initiated in the arterial system or in the tissues. When the cardiac output is decreased below normal—a condition often accompanied by reduction of blood in thoracic veins—reflexes are set up which increase the peripheral resistance in most parts of the body. Kidney blood flow is usually reduced in such a situation. This will lead to reduction in kidney function and possibly to reduced urine volume. This is one explanation given in the past (33) for the reduction in urine volume and kidney function resulting from stresses reducing cardiac output. There is also evidence of increase in production of antidiuretic hormone (34). The receptors initiating these actions are probably the arterial pressor receptors and possibly receptors affected by reduced blood flow in vital organs. In any condition, therefore, that causes reduction in the blood of the thoracic veins leading to antidiuresis, it is necessary to consider to what extent reduced cardiac output is the cause of the reduced urine volume. Sieker *et al.* (32) report the kidney clearance is not affected by the diureses they obtained resulting from increased thoracic vein

filling. It is quite possible that conditions can exist where kidney clearance could be unaffected in the reverse situation—*viz.* the antidiureses accompanying a decreased filling of the thoracic veins. However, this would not be true in all circumstances, and a reduction in kidney clearance in a given situation would suggest operation of reflexes initiated on the arterial side. For convenience such reflexes will be referred to as "arterial" and reflexes initiated on the venous side will be referred to as "venous." One other point must be understood. These volume receptors could be stretch receptors responding to dilatation of the vein wall or they might actually be pressure receptors—such as discs between the circular layers of the veins—responding to venous pressure but indirectly indicating stretch because of the elastic properties of the vein wall. Receptors can also be "in parallel" and in "series" with the muscles of the vein. The information given by the "in parallel" receptors as well as that from the pressure receptors would be greatly modified by the tonus of the vein muscles. This has been shown to be the case for the pressoreceptors located in the carotid sinus (35). This must be kept in mind in considering effects of venous congestion with this hypothesis. Henry *et al.* (36) review their recent work designed to locate the vascular areas in the thorax concerned with the production of diuretic responses. Partial obstruction of the pulmonary veins causes diuresis. The authors also sought to locate the nerve concerned by nerve block experiments. They conclude that the vagus is the most likely route of afferent impulses passing to the brain to set up this reflex.

Birchard *et al.* (37) had subjects drink one liter of water after a liter of 2 per cent NaCl had been given intravenously. The ingestion of water was followed by excretion of a relatively dilute urine with a two- to four-fold increase in flow. This took place when extracellular fluid tonicity must have been such as to promote relative oliguria. The results cannot result from action of osmoreceptors and suggest participation of some volume receptor. Rosenbaum *et al.* (38) maintained a water load (1,500 cc. initial dose) in subjects for 4 to 9 hr. and followed water and salt excretion. When the subjects remained seated the rates of urine flow and sodium excretion steadily declined; when the subjects subsequently reclined augmentation of water and sodium occurred. The magnitude of the diuresis was increased when dietary intake of salt was large and decreased when antecedent salt intake had been restricted. The ingestion of NaCl resulted in increased urine flow and solute excretion.

Fitzhugh *et al.* (39) studied the effects on renal function of tourniquet trapping of blood in the legs. There was slight but significant fall in cardiac output and definite decreases in renal plasma flow, urine flow, and sodium excretion. The reduction in renal blood flow could be part of a general vascular adjustment to maintain blood flow through vital organs, the receptors for this being in the arterial system. Reduced kidney function could result then from reduced blood flow. It is possible too that "venous" reflexes could play a part here. A similar situation is probably present in the condi

tion produced by Farber *et al.* (40) who blocked the venae cavae in different situations by means of a balloon attached to a catheter. This undoubtedly reduced the actively circulating blood volume and could lead to the observed reduction of renal plasma flow as a result of "arterial" reflexes. They found also decreases in excretion of Na, Cl, and usually of water. It is difficult to estimate to what extent these changes would be attributable to the circulatory adjustments and whether "venous" reflexes resulting from reduced blood in thoracic veins could have contributed to the antidiuresis. Wilkins *et al.* (41) studied the effect on renal function of venous congestion of the limbs on supine subjects. This resulted in reduction in urine volume and little change in Na excretion. Pulse rate increased so that there was some circulatory stress so that "arterial" reflexes probably play a part here. The authors discuss the possibility of "venous" reflexes operating also. Similar results were obtained in a subject two weeks after lumbodorsal sympathectomy indicating that the effector mechanism is not the sympathetic or at least not entirely so.

Borst (26) reports observations on various clinical conditions bearing on the relationship of blood volume to urinary output of salt and water. His findings indicate the operation of some mechanism, sensitive to the blood volume, that modifies the urine volume. He rules out central venous pressure as a determinant of urine volume on the basis of the observation that a patient in moderate heart failure when given digitalis has a marked diuresis preceded by a fall in central venous pressure. This argument must be considered very seriously; alteration in the tonus of the vein musculature noted above is an unknown factor that might play an important role here. Nobel & Taylor (42) demonstrated an antidiuretic substance in the urine of subjects who fainted as a result of venesection or from other causes.

Hamilton *et al.* (43) gradually constricted the mitral orifice in dogs. They found creatinine and PAH^2 clearances and venous pressure not markedly abnormal. There was, however, retention of sodium and ascites formation. They cite evidence indicating that the posterior pituitary and adrenal gland may be involved. This is a complicated situation in which "venous" reflexes might operate. A similarly complicated situation of this type is that reported by Barger *et al.* (44).

Water excretion by kidney in general.—Dicker (45) describes a sensitive method for assay of very small amounts of antidiuretic activity making use of a device for maintaining a constant water load in rats (46). Ginsburg & Heller (47) measured the antidiuretic activity of blood taken from various regions of the vascular system in rats. They used a rat assay method developed by them (48). The blood taken from the external jugular was five times more potent than arterial blood. Hepatic and renal vein blood was lower than arterial. The same authors (49) followed the decrease in potency of blood from rats injected intravenously with vasopressin. The fall followed an exponential course. Removal of the kidneys and tying the celiac and mesenteric arteries greatly retarded the fall in antidiuretic activity. Bernstein

et al. (50) find a normal diuretic response to intravenous 5 per cent glucose solution in patients with cirrhosis of the liver. This normal reaction points against hypersecretion or impaired inactivation of ADH[2] in these patients. Stein *et al.* (51) find no greater amount of ADH in the blood of patients with hepatic cirrhosis than in that of all subjects with clinical disorders. There was no relation between the retention of water and ADH activity of the blood. White *et al.* (52) find that the rate of inactivation of beta-hypophamine (Pitressin) in patients with hepatic cirrhosis is the same as that of normals and this tends to exclude a decreased rate of inactivation of ADH as factor in water imbalance in this disease.

Hellmann & Weiner (53) found an increase in antidiuretic substance (rat assay) in the urine of men subjected to exposure to high temperature for periods of 45 to 120 min. The authors mention the desirability of repeating the experiments on subjects maintained in positive water balance. This would be desirable in order to decide whether this response is attributable to osmoregulation or has something to do with volume control. Ullmann (54) found that subjects on going from sea level to 11,000 feet had reduced water output for two days. The same inhibition occurred on returning to sea level. Friedberg *et al.* (55) report a study of a subject who exhibited periods of antidiuresis during water diuresis induced by continued water loading. Renal plasma flow was markedly diminished during the periods of low urine output. The authors consider the possibility for an emotional origin of the reaction although there was no clear cut evidence for it.

Mirsky *et al.* (56) found an increased secretion of an antidiuretic substance as a result of noxious stimuli (electric shock in the rat, ischemic pain in man). This also occurred in hypophysectomized rats The authors conclude that a neurohormone with antidiuretic properties is secreted by the hypothalamus in response to noxious stimuli. It is of interest to compare these findings with those of Ushkow & Birnie (57) who could not find antidiuretic substance in the blood of hypophysectomized rats; presumably these had not received noxious stimuli. Eversole & Giere (58) found that 5 min. exposure of rats to ether causes an increase in the antidiuretic activity of their blood. It would be interesting to see whether this result would occur in hypophysectomized rats. Nichols (59) reports that crude dialized and concentrated human urine when injected intravenously in the human produces a marked general system reaction with complete renal shut-down. This preparation produces a diuresis in the dog. Croxatto *et al.* (60) examine the possible role of the adrenal cortex in renin diuresis, since this is noticeably modified by intake of NaCl. In another paper (61) from the same laboratory is the report of an antidiuretic factor liberated from blood serum by the action of pepsin.

Inorganic Salt Metabolism

Many of the papers in this field are difficult reading. This stems largely from the desire of many workers to report their findings in terms of theoreti-

cal mechanisms operating in the kidney. This was easy when dealing with the excretion of waste substances, which are handled by the kidney in accordance with a very simple rule, but homeostasis is a complicated business, as workers with artificial kindeys know very well (62, 63). These theoretical mechanisms are derived from clearances—which are abstract values—and, until the validity of such derivations is proven, people are still talking of abstractions even if they name them concrete processes. The theorists have got far from the naively simple model of Cushny, but still they have trouble predicting what the kidney will do when a new situation is tested. Usually then they indulge in what Hemingway[5] defines as "unsoundness in our abstract conversation." The result doesn't make good reading.

General factors influencing excretion of salt.—Thompson & Barrett (64) report the sodium and water excretions of hydropenia dogs subjected to osmotic diuresis (mannitol or glucose) or to reduction in renal blood flow (Dotter-Lukas balloon). Sodium excretion was reduced practically to zero when the glomerular filtration rate was markedly diminished. Urbach *et al.* (65) studied the renal excretion of solutes after oral administration of a standard amount of water. They found that water diuresis may induce changes in excretion of urinary solutes of some magnitude. Potassium, sodium, and chloride excretion fell considerably 3 hr. after water administration. Birchard & Strauss (66) reported on diuretic response to drinking 1 l. of saline by seated subjects. They report that this did not result in a water diuresis although their records show the usual small increase in urine volume ordinarily obtained. Sitting quietly presumably promotes passage of fluid into the interstitial space of the dependent parts. If the subjects had been loaded with saline the previous day they showed greater increases in urine volume. Bucht *et al.* (67) find that renal blood flow and function are not affected by light exercise, but with heavier work both the blood flow and the Na excretion decreased 20 per cent. Bass (68) reports that exposure of humans to cold brings about increased excretion of Na and Mg but not of K, and this occurs when the diuresis which usually accompanies cold exposure does not supervene. He concludes that these two responses are probably attributable to independent mechanisms. Forster (69) reviews renal function in marine teleost. The electrolyte transport in the aglomerular tubules of the goose fish is described by Forster & Berglund (70).

Kanter (71) studied the reactions of dogs to imposed salt loading. He found that some dogs corrected the imposed imbalances by drinking while others used their kidneys to correct the situation. The differences in drinking among the dogs was not attributable to differences in concentrating capacity of their kidneys. The kidneys themselves do not act as primary thirst receptors, for a dog with or without kidneys will drink similar amounts of water in response to a given salt load. Green *et al.* (72) have studied salt excretion in normals and in hypertensive patients. They group hypertensives into high-

[5] From *Death in the Afternoon*.

salt excretors and normal-salt excretors. The former represent an early stage of hypertensive disease and the latter a later stage.

Kaplan *et al.* (73) determined the effect of unilateral division of the splanchnic nerve on renal excretion of electrolytes. The section was effected in the thorax. The denervated kidney excreted more NaCl and water than the control. The difference was in large measure attributable to decrease in excretion of these substances by the control kidney. The authors suggest that blood flow is diminished on the control side as a result of reflex maintenance of blood pressure which would tend to be lowered by the splanchnicotomy of the opposite side. Surtshin & Hoeltzenbein (74) denervated one kidney of dogs and collected urine from it and from the normal paired kidney. They studied the excretions of Na during hydropenia, water diuresis, and NaCl diuresis and failed to find any consistent differences in Na excretion by the innervated and denervated kidneys. Page *et al.* (75) made observations on dogs with unilateral splanchnic nerve resection and determined the effect on renal excretion of Na. There is considerable variation in their results although the denervated kidney tended to excrete more Na in the majority of the animals.

Sellwood & Williams (76) discuss the relation of Na reabsorption to oxygen consumption. Ullmann (54) reports a reduction in salt excretion on going to altitude. Ek & Josephson (77) find that beer contains an agent appearing during fermentation that increases the output of water and Na and decreases K excretion. This agent is not alcohol. This agent also increases the inulin clearance (78).

Action of mercurial diuretics.—Rice *et al.* (79) find that the salt depleted dog excretes less salt than the normal, when both are given full mercurialization. A later paper from the same laboratory (80) reports the effect of mercuhydrin upon tubular reabsorption of electrolytes in dogs infused with sodium nitrate. The authors conclude that this drug causes a primary inhibition of Cl reabsorption and other effects are secondary. Welt *et al.* (81) followed the rates of excretion of water and of solutes after administration of a mercurial diuretic in normal subjects. They suggest that Hg acts in an area of the nephron where water is dependent on and secondary to the active reabsorption of solutes. Farah & Koda (82) studied the influence of plasma electrolyte concentration on the mercurial diuresis in the dog. When the plasma Na concentration was reduced to 80 to 90 millimoles per l. the animals became refractory to mercurials but still responded to an injection of a toxic dose of cyanide. Cohen & Weber (83) examined the kidneys of rats that had been treated with mercurials and those that had been treated with alloxan. Kidney slices from these animals did not show a diminished uptake of oxygen. Labeled inorganic phosphate uptake of the slices was decreased in rats treated with mercurials, but was normal in alloxanized rats. Mustakallio & Telkkä (84) promote the view that mercurial diuretics produce their effect by inhibiting succinic dehydrogenase. They report their results of a histo-

chemical study of succinic dehydrogenase activity before and after mercurial administration. They find the biggest change in the distal segment of Henle's loop. Moderate reduction occurred in the convuluted tubules.

Action of hormones on salt excretion.—Leaf *et al.* (85) gave long-acting posterior pituitary extract to subjects for two to four days. It was found that normally hydrated subjects showed water retention, serum dilution, and definite increase in excretion of Na and Cl on the second and third day. These changes were prevented by restriction of fluid intake during beta-hypophamine (Pitressin) administration. The finding that imposed fluid retention causes increase in excretion of Na and Cl is puzzling. Electrolyte disturbances in adrenal disease is reviewed by Knowlton (86). Kellogg & Burack (87) find that adrenalectomized rats can markedly increase their urine flow and urinary excretion of Na and Cl in response to a load of isotonic saline even when they can no longer increase their urine flow in response to a load of distilled water. Beatty *et al.* (88) describe a water tolerance test for functioning adrenal cortical tissue in the rat. The test should be of value in determining the existence of hypertrophied accessory adrenals after adrenalectomy. Holland & Stead (89) compared effects on electrolyte excretion of adrenal cortical agents and of motionless standing. The fall in electrolyte excretion caused by motionless standing could not be reproduced by cortical agents. It is concluded that these urinary changes accompanying standing are not mediated through the adrenal cortex. Davis & Howell (90) studied the action of cortisone on water and electrolyte balance in dogs subjected to thoracic inferior caval constriction in addition to adrenalectomy. These authors conclude that cortisone influences Na excretion by two opposing actions: (*a*) augmentation of Na reabsorption by a weak effect on renal tubular transport and (*b*) increased Na loss by elevated glomerular filtration rate.

Farrell & Richards (91) isolated a substance from adrenal venous blood of dogs which is 25 times as potent as DOCA[2] in producing Na retention in adrenalectomized rats. Luetscher & Johnson (92) find in the urine of nephrotic children a corticoid with sodium-retaining activity 15 to 20 times greater than that of DOCA. This was not found in the urine of normal children. Dempster & Graber (93) studied the effect of unilateral adrenalectomy on homolateral renal function in dogs using the opposite kidney as control. Their findings lead them to suggest the possibility of an intimate adreno-renal hormonal relationship. Davis *et al.* (94) studied renal functions, electrolyte and water metabolism in adrenalectomized hypophysectomized dogs. Both thyrotropin and growth hormone increased GFR[2] and RPF[2] in these animals. They find that altered renal circulation characteristic of the hypophysectomized animal cannot be attributed to loss of ACTH[2] only. Three other hormones are involved.

Excretion of bicarbonate.—Recent work in this field is reviewed by Robinson (95) and by Gilman & Brazeau (96). Pitts *et al.* (97) review recent work from their laboratory on excretion of bicarbonate by the kidney and present

their latest theory of the mechanism of renal tubular reabsorption of bicarbonate bound base. Thompson & Barrett (98) studied the excretion of bicarbonate in dogs subjected to sodium bicarbonate loading. Their results indicate that under ordinary conditions and with elevated plasma bicarbonate the tubular reabsorption of bicarbonate is proportional to the GFR (creatinine clearance). They reduced kidney function by partially obstructing blood flow to the kidneys. This resulted in decreased filtration and increase in the ratio of reabsorption to filtration of bicarbonate. They conclude that the reabsorption of bicarbonate is not inseparably linked to the level of GFR. It is interesting that with this circulatory embarrassment the excretion of bicarbonate was much more reduced than that of creatinine. Relman *et al.* (99) studied the excretion of bicarbonate in alkalinized dogs in which they varied the plasma pH and pCO_2 independently. Increasing pCO_2 with pH kept constant resulted in increased excretion of bicarbonate and increased tubular reabsorption. When the plasma pCO_2 was increased by reducing lung ventilation the plasma pH fell towards normal, bicarbonate excretion remained the same, and tubular reabsorption increased. The authors suggest that bicarbonate reabsorption is related to carbon dioxide tension "in a manner which tends to preserve the neutrality of the reabsorbate and the extracellular fluid." Brazeau & Gilman (100) studied bicarbonate excretion in alkalinized dogs in which plasma bicarbonate was elevated by infusion of $NaHCO_3$ and plasma CO_2 tension was varied by controlled ventilation with air or CO_2 mixtures. The rate of renal tubular reabsorption of bicarbonate was found to vary directly with plasma CO_2 tension over a wide range. The authors suggest that bicarbonate reabsorption is entirely dependent on the exchange of hydrion from carbonic acid in the tubule cell for the fixed base of filtered bicarbonate in the tubular urine. As far as urinary excretion of bicarbonate is concerned their figures agree with others; this is dependent on both the pH and pCO_2 of the plasma. Dorman *et al.* (101) studied excretion of bicarbonate in dogs infused with sodium bicarbonate and ventilated with air or 12 per cent CO_2. Their findings are similar to those cited above—reabsorption of bicarbonate is related to plasma pCO_2. The hypothesis is proposed that a mechanism involving exchange of hydrions for basic ions operates throughout the renal tubule.

Dorman *et al.* (102) investigated in dogs the relationship between urinary CO_2 tension and urinary buffer concentration. They raised the plasma phosphate concentration by infusion and infused bicarbonate at a rate that maintained the plasma level constant. The urines were always alkaline. The results indicated a relationship of urinary CO_2 tension to urine flow and a poorer correlation of urinary CO_2 tension to phosphate excretion. Sullivan & Dorman (103) maintained chronic respiratory acidosis in dogs for twelve hours to two weeks. They found that renal bicarbonate reabsorption was greater than in acute respiratory acidosis and this increment was a function of the duration of acidosis.

Dowds *et al.* (104) studied Na and K excretion in dogs in which they produced increased pCO_2 by having them rebreath. With the development of pronounced hypercapnia (15) per cent of inspired air) the urine showed increased hydrion concentration and decreased excretions of Na and K. McDonald *et al.* (105) studied the electrolyte blood concentrations and excretions in human subjects hyperventilated for 3 hr. by passive respiration. With the rise in urinary pH there was a rise in the bicarbonate to cation ratio. At the same time there was a fall in the Cl to cation ratio.

Nadell (106) studied the effects of administration of carbonic anhydrase inhibitor "6063" on urinary excretion by normal man and in two patients with pulmonary acidosis. The electrolyte changes in both groups were similar. Administration of the inhibitor caused increase in urinary pH, CO_2, Na, K, and phosphate and a fall in urinary ammonia. Bühlmann *et al.* (107) review the subject of the effect of carbonic anhydrase inhibitors on kidney excretion and report results which they have obtained with its use in men. The same group (108) administered it in higher doses to dogs and obtained general depression of all urinary function resembling chronic nephritis. It is noteworthy that this occurred without particular morphological changes in the kidney. The report of Dufault & Tobias (109) is of interest. They report two cases of renal failure resulting from continued alkalosis with renal function returning to normal on cessation of alkaline intake.

Acid-base metabolism and ion exchange mechanisms.—Considerable experimental work in this field has been carried out by studying the effects of alterations in intake of potassium. Berliner *et al.* (110) reviews some aspects of this interesting relationship, and later the same group discuss the problem largely on a theoretical basis (111). Liddle *et al.* (112) report that oral administration of K salts to humans consistently increases Na excretion. This increase is greater if Na retention has been induced by cortisone. The authors suggest two possible mechanisms: displacement of body Na by K, and suppression of renal tubular H-Na exchange. Fuller & MacLeod (113) report depression of bicarbonate reabsorption by hyperkalemia even when plasma bicarbonate levels are maintained by infusion. The K effect on bicarbonate reabsorption is not as marked as in animals with lowered plasma bicarbonate.

Milne *et al.* (114) report recent work on the potassium-hydrion relationship in states of K-depletion in man. Potassium excretion in response to administration of a standard amount of it depends on the degree of depletion of this metal rather than on K plasma level which changes relatively little with depletion. Hyperventilation alkalosis of the K depleted subject resulted in an alkaline urine with little increase in K, whereas in the normal K increases markedly. Squires *et al.* (115) find on the basis of a study of human subjects on a low K intake that the kidney can effectively conserve K when the body is depleted of it. Evans *et al.* (116) showed that during dietary K depletion the kidney is capable of efficient conservation of this cation despite conditions which ordinarily result in increased urinary K loss, i.e., hyper-

ventilation, osmotic diuresis, and carbonic anhydrase inhibition. The authors conclude that the results are compatible with a theory that there is competition between K and hydrogen ion for exchange with Na in the distal tubules of the kidney, but show that there is no compulsion that this exchange should occur when the availability of both K and hydrogen ion is reduced. Franglen *et al.* (117) studied the effect of experimentally produced alkalosis on excretion of K. Alkalosis was produced by differential peritoneal dialysis, intravenous infusion of sodium bicarbonate, and by hyperventilation. Potassium excretion increased in the alkalosis produced by all these means despite a negative balance for this ion. The rate of excretion of K exceeded the calculated rate of glomerular filtration of this ion so that it was concluded that tubules secreted it. The authors conclude that the excretion of electrolytes during alkalosis cannot be described "in terms of fixed thresholds or by absolute reabsorption maximum, as required by systems which imply an excretion of ions related functionally to the filtration rate."

Mills & Stanbury (118) studied the excretion of K and hydrion in man for periods of 6 to 8 hr. duration in which the usual rhythms of habit and environment were largely excluded. The reciprocal relationship between K and hydrion excretion was always observed. The authors suggest that the rhythmic diurnal change in hydrion excretion results from rhythmic variation in secretory activity of the distal tubule cells. Longson & Mills (119) had human subjects breath 5 to 6.5 per cent CO_2 for 2 to 3 hr. at a time in the morning when, in control experiments, outputs of Na, K, and bicarbonate were rising and phosphate, acid, and NH_3 falling. All the morning tides in excretion rates, except that of phosphate, continued exactly as in controls. The alveolar pCO_2 was definitely increased. It would be interesting to test the theory of control of bicarbonate tubular reabsorption by plasma pCO_2 in experiments of this type. The authors feel that respiratory acidosis cannot be the cause of the usual nocturnal aciduria.

Schlegel *et al.* (120) studied the relationship between pH of the urine and Na and K excretion. They conclude that Na-K excretion is related to the variability of the pH of the urine of a given individual. Subjects excreting a low amount of Na tend to have a constant urinary pH which ranged from person to person between 4.8 and 6.0. Relman & Schwartz (121) administered sodium sulphate to Na-depleted subjects and to those in normal Na balance. Infusion of sodium sulphate in the controls produced little change in urinary pH and ammonia excretion. In contrast the urine of the salt depleted subjects decreased in pH and increased in NH_3 content. The authors propose that urine acidification under these conditions is the result of increased exchange of Na for hydrogen or ammonium ions or both. Orloff & Berliner (122) measured urinary pH and excretion rates of weak electrolytes like quinine, quinacrine (Atabrine), and NH_3 and propose a complex relationship between these. Black & Mills (123) studied the output of electrolytes after moderate loading with various salts. NaCl , $NaHCO_3$, KCl, or $KHCO_3$ were given at

bedtime, and the excretion during the night was determined. Hydrogen ion output was depressed by both K and HCO_3. Sodium salts increased Na output slightly but did not alter other outputs particularly. Potassium increased output of K and even more of Na. The results are discussed in terms of ion exchange mechanisms. Heller *et al.* (124) injected magnesium sulphate intravenously at constant rate in humans and found a slight decrease in RPF and GFR. There was increased urinary excretion of Na and Cl and decreased excretion of K. The clearance of Mg increased fivefold as a result of the injection. The results suggest that Mg may be involved in an ion exchange mechanism. Cort (125) subjected dogs to NH_4Cl acidosis and determined the effect of dehydration on the urinary electrolyte adjustment. The adult dog showed a marked decrease in Na excretion when dehydrated despite coexistant acidosis.

Schwartz *et al.* (126) administered acids to subjects on a low Na diet and determined the excretion of the pertinent electrolytes. They found that ammonium excretion was relatively greater and more prompt than in normals and that the initial renal ammonium response was directly proportional to the rate of excretion of the loading anion and was not related to serum or to urine pH. They also found that Na constituted only a small proportion of all cation excreted. Nicholson (127) produced a mild nephrosis in one kidney of the dog by local injection without affecting the other kidney. The only observed difference in the urine of the two kidneys was an increase in pH of that from the damaged kidney, although the ammonia excretion from it was equal or greater than that of the other. It can be concluded that the acidity of the urine cannot be the major factor in determining the amount of ammonia formed by the kidney.

McNamara & Barnett (128) find that the administration to premature infants of the Na salts of the unreasborbed anions PAH and thiosulphate results in the renal excretion of the anions principally covered by Na. This takes place despite the prematures' low glomerular filtration rate which in other situations tends to promote the balancing by K. Tudvad (129) found that the physiologic acidosis of the premature infant cannot be explained as a disturbance in tubular bicarbonate reabsorption. The premature infant kidney is capable of tubular secretion of K. Cort & McCance (130) find that puppies are less able than adult dogs to correct an imposed acidosis by urinary excretion. They excrete less free acid and practically no ammonia. Most of the anions were excreted in association with fixed base.

Smith & Schreiner (131) studied renal outputs in two cases of hyperchloremic acidosis. They discuss possible defects in renal function that may cause this condition and suggest that it is most likely attributable to combined defects in reabsorption of bicarbonate and secretion of hydrion. The same authors (132) demonstrate the inherited nature of this condition. Sirota & Hamerman (133) reported their findings in a thorough study of a case of renal acidosis (adult Fanconi Syndrone). Jackson & Linder (134)

review the various syndromes found clinically that show disturbances of innate renal tubular function.

Coulson & Hernandez (135) report that the kidney of the alligator excretes ammonia into an alkaline urine and excretes bicarbonate to conserve chloride.

Other inorganic substances.—Henry *et al.* (136) using labeled P to identify administered phosphate found no difference in the way the kidney handled it from that of plasma acid-soluble inorganic phosphorus. Taugner *et al.* (137) report that inorganic phosphate may be secreted by the renal tubules as the result of the metabolism in them of organic phosphates. The tubules, however, do not transfer inorganic phosphate from blood to urine. Jacobs *et al.* (138) studied phosphate excretion by the kidney making use of tagged injected phosphate to distinguish between excretion of endogenous and exogenous phosphate. They conclude that there may be a small amount of organic phosphorus compounds with a low renal filterability. After treatment with parathyroid extract both the inorganic phosphorus preexistent in the plasma and the injected inorganic phosphate are excreted in equally increased degree. If phosphate in the plasma exists in two different physicochemical states the hormone acts on them equally.

Recent work on the action of the parathyroid on the kidney is reviewed by Bartels (139). Davies & Gordon (140) show that the magnitude of the effect of parathyroid hormone on urine phosphate of parathyroidectomized rats depends on the serum phosphate level. It appears that only those animals having a serum inorganic phosphorus above 8 mg. per cent can be expected to show much effect. Talmage (141) reports that in rats excretion of calcium is increased during the first 12 hr. after parathyroidectomy. During the following 12 hr. excretion is the same as in controls. Using radioiron Closuit *et al.* (142) studied the excretion of iron by the kidney. The rate of excretion was roughly proportional to the amount injected. Three to 30 per cent of the injected material was excreted in 1 to 2 hr. Ingbar (143) shows that cortisone increases the renal excretion of iodine in hypophysectomized rats.

Intrinsic Metabolism of the Kidney

A great deal of work is appearing on the metabolic processes of the kidney concerned with effecting its specific functions in homeostasis and in removing wastes. Experimental procedures range all the way from work with intact subjects involving conclusions derived from function tests down to *in vitro* observations in enzyme reactions of kidney homogenates.

General metabolic reactions found in the kidney.—Goldfarb *et al.* (144) measured the rate of uptake of injected labeled phosphate by the organic phosphorus compounds of the kidney. The blood was drained from the renal vein so there could have been no involvement of other organs. The uptake of the labeled P by ADP-ATP[2] and by glucose-1-phosphate is very rapid, more so in cortex than in medulla. They suggest that glucose-1-phosphate

is derived from glycogen via the phosphorylase reaction. The authors feel that the very low P uptake by the glucose-6-phosphate indicates that most of this compound found in the kidney is formed elsewhere in the body and carried to this organ by the blood. Taugner *et al.* (145) report that when certain organic phosphate compounds are infused there is indication of tubular secretion of inorganic phosphate in which tubule phosphatases appear to be involved. Eger *et al.* (146) report that after adrenalectomy there is a decrease in phosphates in the kidney. Beaulieu & Dallemagne (147) measured the concentration of citric acid in the kidneys of rats poisoned with fluoracetate. They found a marked increase in concentration of this compound. If the tissue is allowed to stand after removal from the animal this concentration diminishes slowly. In the liver the citric acid disappears very rapidly on standing.

Reference can be made here to the mechanism proposed by Wirz whereby the kidney concentrates the urine. This involves a physicochemical process known as the hair-pin turn theory. He (148) reviews evidence for this based on direct cryoscopy carried out on frozen kidneys. Subsequently (149) he gives results of osmotic pressure measurements of blood and urine obtained from the tip of the papilla in the golden hamster, a species having a favorable anatomical arrangement for obtaining samples of these by micropipettes. He reports that when the urine is hypertonic the blood is almost equally so, a finding supporting the hair-pin theory.

Ullmann (150) studied kidney excretory function of subjects breathing 8 or 10 per cent oxygen. No change in function could be directly attributed to the influence of oxygen lack on the kidney itself. Alterations of renal electrolyte output were a result of disturbances in acid-base balance incidental to hypoxia. Miller (151) studied renal tubular transport maxima, both reabsorptive and excretory, in human subjects before and after induction of renal hyperemia. Renal hyperemia was produced by aminophyllin and by typhoid vaccine. Hyperemia was associated with increases in tubular transport maxima both for PAH and for glucose. The author believes that some nephrons are not perfused under standard testing but are under the conditions imposed by him. Deyrup (152) studied conditions which can reverse the rapid hydration of kidney slices that occurs under anoxia. The slices readjusted to control content of water when they were incubated in oxygen and 0.15 M NaCl, but this does not occur in isotonic glucose. Ruskin *et al.* (153) report that succinic dehydrogenase activity is reduced in the kidney the renal artery of which is partially occluded (Goldblatt technique) whereas the contralateral untouched kidney shows no change in activity.

Whittam & Davies (154) studied the water, Na, and K uptakes of kidney slices under aerobic and anaerobic conditions using alpha-oxoglutarate as a substrate. The prevention of swelling and the production and maintenance of Na and K concentration gradients are dependent upon a supply of energy from respiration. Later (155) they report on the uptake and to-and-from

movements of Na and of K by kidney slices using radioactive tracers under various metabolic conditions. Under anaerobic conditions the uptake rate was about 75 per cent of the aerobic rate for both cations. The maintenance of the physiological concentration gradients of these ions depends on respiration. In oxygen the turnover rates were not affected by the absence of substrate or the presence of 2:4 dinitrophenol despite major changes in the respiration rate. Mudge (156) studied the uptake of K by kidney slices. He found that when the slices were incubated in oxygen there was a rapid accumulation of K from the medium into the cells. When a steady state had been reached labeled potassium (K^{42}) was added to the system. The radioactive K rapidly exchanged with the intracellular K, and equilibrium was reached in 60 min. When incubated anearobically the kidney slices failed to accumulate K, so that the average concentration at the end of 60 min. was 18 m. eq./kg. compared to 69 m. eq./kg. for slices in oxygen. When labeled K was added it exchanged promptly with a part of the intracellular ions, but at equilibrium only 55 per cent of the tissue K had the same specific activity as that of the K of the medium. There is then a definite effect of the metabolic rate of the tissue on the uptake of K and its retention by the cells. He also found that the movement of K into or out of the cell is independent of the movement of Na induced by varying the concentration of this cation in the medium. Sodium exchange shows no such relationship to metabolic activity.

Taggart *et al.* (157) find that PAH transport in rabbit-kidney slices is maximal only when tissue potassium and Na are close to normal values. The replacement of Cl in the medium by various other anions inhibits transport to a variable degree. The degree of inhibition observed with each anion appears to be related to the position of the anion in the lyotropic series. Judah & Rees (158) find that rabbit-kidney mitochondria are unable to activate octanoate oxidation in the presence of ATP and require co-oxidation of an intermediate of the citric acid cycle.

Since mitochondria are the site of respiratory activity and oxidative phosphorylation of the cells (159) and since oxidation phosphorylation seems to be linked with active transport (154), it is reasoned that mitochondria are closely associated with secretory activity in the cells. The complex structure of mitochondria is described by Palade (160) in a paper that includes descriptions and illustrations of kidney mitochondria. Schneider (159) in a paper on the biochemistry of mitochondria reviews enzymatic activities connected with those of the kidney. Bartley & Davies (161) have studied the concentration gradients between mitochondria and media of such ions as Na, K, hydrogen, and phosphate. They give as evidence of active transport of these ions, the increase in the concentration gradient effected by active metabolism over the gradient found in the absence of metabolizable substrates. Differences in pH up to 0.4 unit between mitochondria and the suspending media were found during active metabolism but were abolished by incubation without substrate.

Bartley (162) studied the action of washed sheep kidney particles (mitochondria and nuclei) on thiamine derivatives in the presence of labeled phosphate. In a subsequent paper (6) he reports phosphopyruvate is formed by these kidney particles during oxidation of various Krebs cycle compounds. The phosphopyruvate appears to have a high turnover rate. Inorganic phosphate is not the immediate precursor of the phosphate group in phosphopyruvate. The author suggests that ATP supplies this.

Effects of loading with one or more excreted substances.—Engström & Josephson (163) report that in rabbits injected with iodopyracet (Diodrast) the iodine could be observed microscopically inside the tubule cells by the use of x-rays provided a large amount of diodrast was injected. Josephson & Kallas (164) determined the concentration of diodrast iodine in the kidney after injection of varying amounts of it. This was done in normal rabbits and in those given experimental uranyl nephritis and after injections of PAH, carinamiate, and mersalyl (Salyrgan). The authors feel that the results indicate that an accumulation of diodrast in the tubule cells occurs when the cells are offered more diodrast than they can excrete, that is when the plasma concentration exceeds the depression limit.

Josephson *et al.* (165) studied simultaneous excretion of diodrast and PAH in man. When the plasma concentration of one of the substances was increased, the percentage renal extraction of both was equally depressed. With increasing plasma concentration, the tubular excretion of diodrast increases relative to the PAH excretion. The authors conclude that the two substances are probably excreted by the same mechanism which at high plasma concentrations can transport more diodrast molecules than PAH. In the rabbit (166) when these are given simultaneously in high concentrations each depressed the excretion of the other. However, more diodrast than PAH was excreted, and the sum of the two was greater than if PAH were given alone. In a subsequent report on excretion of these compounds in rabbits Josephson (167) reports that no blockade could be achieved in tubular excretion of these when given singly even though the plasma concentration was enormous, although they mutually depress each other if given together. Priscoline (2-benzylimidazoline hydrochloride) is secreted by the tubules but does not compete with PAH (168). Tetraethylammonium is secreted by the tubules (169). The transport of phenol red in the flounder renal tubule is described (170).

Josephson & Kallas (171) studied the simultaneous excretion of creatinine and inulin in the rabbit. The clearances of these were usually about equal. The authors state that the clearances are independent of plasma concentration. However, their figures show marked lowering of clearances at high creatinine plasma levels. Unfortunately they produced these high concentrations only towards the end of their experiments and "when the animals were tired and when the blood pressure was probably low." This part of the work should be repeated under controlled conditions. Sosnowick (172) reports that in the albino rat given a considerable urea load the urea-inulin

clearance ratio may exceed one when diuresis is steady or falling. The author advances the hypothesis that urea may at times diffuse from blood into the tubular fluid. It is hard to figure a condition which would give the needed concentration gradient for such a process. Ogden & Moore (173) examine the problem of back diffusion of urea through the tubular epithelium.

Specific inhibitors of renal secretion.—These have greater action than what would be accounted for on a mass action competitive basis and are reviewed by Beyer (174). Beyer *et al.* (175) examined the competitive inhibitory action and renal clearance of a series of *p*-alkylsulfonamidebenzoic acids. Sperber (176) reports on his study of competitive inhibition of phenol red secretion by other members of the sulphonephthalein series. Some like bromcresol green markedly reduce phenol red excretion although they themselves are excreted in small amount. The author concludes that the division between specific and unspecific action is an arbitrary one.

Campbell (177) finds that phenylbutazone causes retention of salt and water in most subjects. Tubular secretions of PAH is markedly depressed. King (178) studied the effect of phenylbutazone on excretion of PAH and thiosulphate in the dog. Thiosulphate excretion is not affected by this drug. The inhibition of excretion of PAH by phenylbutazone is reversed by the simultaneous administration of acetate. Yü *et al.* (179) studied the effect of phenylbutazone on the ordinary renal functions of gouty subjects. GFR was little affected. The authors feel that this drug acts on tubular transport mechanisms, inhibiting the reabsorption of urate and the secretion of PAH and increasing reabsorption of Na and Cl. Farah *et al.* (180) found that fluoracetate reduced renal blood flow, ordinary clearances, and Tm in dogs (glucose and PAH). Sodium acetate administration protected against the effects of fluoracetate on PAH excretion, but not against its effects on glucose reabsorption.

Enzymatic activities of the kidney.—Oliver (181) published an article reviewing work correlating postmortem morphological findings with premortem alterations in function. In regenerating kidneys he shows histochemical evidence based on findings in matching areas that the absence of lipase and of phosphatase in tubule cells is associated with absence of mitochondria. The same author (182) reviews experimental work in rats poisoned with sublimate that show the same association. Wachstein & Meisel (183) made a histochemical study of succinic dehydrogenase in the rat kidney. All tubular segments of the nephron located in the cortex were found to be active. In tubules poisoned by *d-l*-serine or meralluride (Mercuhydrin) the normal staining pattern disappeared rapidly. Regenerating tubules showed enzymatic activity after 5 days although even after 26 days a normal staining pattern was not seen. Another study of the action of mercurials on succinic dehydrogenase has already been mentioned (84).

Taggart (184) reviews present theories of metabolic processes taking part in tubular secretion. He presents possible chemical reactions involving CoA^2,

acetate and organic phosphate compounds that may be involved in the tubular transport of carboxyl compounds. Schachter & Taggart (185) report that benzoylthioester of CoA is an intermediate in the enzymatic synthesis of hippurate by kidney cortex by transfer of the benzoyl group to glyceine. In a later paper (186) these workers report that the enzyme involved is capable of effecting similar transfer to glycine of a variety of aliphatic and aromatic acyl groups. This enzyme is found in liver and kidney and is named by them glycine N-acylase. Wiebelhause *et al.* (187) report that the reaction of acetate with CoA can be inhibited by probenecid (Benemid). The authors feel probenecid acts also on another compound of the PAH system. Graham *et al.* (188) using slices of dog kidney find that small doses of fluoracetate inhibit the action of acetate in stimulating PAH uptakes.

Cunningham & Laskowski (189) report on the presence of two different desoxyribonucleode-polymerases and an inhibitor to one of them in kidney homogenate. Manzini & Zoboli (190) found that barbituate decreased the alkaline phosphatase activity of the kidney. Partial hepatectomy also decreases this kidney phosphatase, but superimposing barbiturate increases the activity. Krause & Powell (191) find that kidney homogenate is able to esterify vitamin A. Heimberg *et al.* (192) present evidence indicating the presence in the kidney of an enzyme that catalyses the oxidation of sulphite to sulphate. Mounter *et al.* (193) describe the preparation of dialkylfluorphosphatase from kidney. They studied the activity of this enzyme under a variety of conditions. Activation and inhibition of this enzyme by metals is reported in a subsequent paper (194). Van Bekkum & Kassenaar (195) report an increase in *d*-amino acid oxidase activity of the kidneys of castrated rats after treatment with testosterone. Sheffner & Bergeim (196) find that increasing the casein content of the diet or adding methionine to the diet increases the *d*-amino acid oxidase activity of the kidney in the rat.

Tabechian *et al.* (197) has studied the metabolism of L-cysteinsulphinic acid by the kidney of the rat using paper chromatography. This acid is considered as an important step in the metabolism of the sulphur amino acids. Reiner & Hudson (198) report on glutamine synthesis and exchange in kidney and other tissue homogenates. Otey *et al.* (199) described a solubilized glutaminase I extracted from kidney homogenate. White & Rolf (200) find that renal glutaminase activity is not changed by hypophysectomy or by adrenalectomy. The lowered ammonia excretion seen in adrenal insufficiency is not attributable to this part of the ammonia forming mechanism. Leuthart & Staehelin (201) studied the synthesis of arginine from citrulline and aspartic acid by kidney enzyme system, which is in the soluble fraction of the cells. They find an intermediate product, identified by paper chromatography, which can be transformed to urea by a liver enzyme.

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CONDUCTION AND TRANSMISSION IN THE NERVOUS SYSTEM[2]

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This review surveys some of the literature which appeared between June, 1953 and June, 1954, although it was found convenient, for purposes of integration, to include a number of earlier references. Because of space limitations certain subjects have been entirely omitted, and the reviewer has selected those aspects of conduction and transmission which especially interest him. During the past two years many new ideas resulted from researches employing the technique of intracellular recording with microelectrodes. This aspect of the subject is featured in this review.

During this period a number of books and reviews were published. Some of these were of a general nature (1, 2) while others were concerned with various specialized phases of the subject (3 to 12).

Properties of the Resting Nerve and Muscle Fiber

Ions and ion movements.—The state of potassium in nerve and muscle fibers has frequently been discussed. Hodgkin & Keynes (13) published their results, already known in preliminary form (14), showing that the bulk of the potassium in axoplasm of *Sepia* axons diffuses at a rate which is consistent with the movement of free ions. The Ling fixed-charge hypothesis was supported by another experiment (15), in which it was demonstrated that K^{42} freshly added to frog muscle, and presumably not yet absorbed in the "energy well," exchanged more readily than the potassium already present in the muscle. It appears likely that Ling's experiment is subject to more than one interpretation. McLennan & Harris (16) employed the rabbit vagus nerve with sheath intact (!) and concluded that only about 36 per cent of the total internal potassium was exchangeable with labelled potassium in the external solution. Since low temperature increased the amount of exchangeable potassium, and since this increment was not exchangeable with external sodium, the authors suggested the possibility of potassium binding by mobile negatively-charged groups.

It is generally considered that sodium is extruded from many living cells against the electrochemical gradient through energy supplied from metabolism. McLennan & Harris (16) confirmed in rabbit vagus nerve a fact which

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[2] The following abbreviations have been used in this chapter: DNP (dinitrophenol); TEA (tetraethylammonium); DFP (di-isopropyl fluorophosphate); e.p.p. (end-plate potential); IPSP (inhibitory postsynaptic potential); TEPP (tetraethylpyrophosphate).

was known for other tissues, that lowering the temperature (from 18° to 0°C.) results in a loss of potassium and a gain of sodium, presumably attributable to a slowing of metabolic reactions. Analysis revealed that low temperature slowed both sodium outflux and potassium influx while leaving unaffected the sodium influx and speeding up the potassium outflux. An increased loss of potassium in resting invertebrate nerve fibers as the result of low temperature was also reported by Shanes (17). Keynes & Maisel (18) calculated the secretory work which would be required to move sodium out of frog muscle at the experimentally determined rate, and concluded that of the energy supplied by resting metabolism only about 10 per cent would be required to extrude sodium at this rate. This does not prove that sodium outflux is an active process, but it gives a reasonable figure which allows sufficient residual energy for carrying out other cellular reactions. The metabolic inhibitor, dinitrophenol, was shown (19) to produce a progressive and reversible decrease in resting sodium outflux in *Loligo* and *Sepia* axons. Moreover, the sodium influx during activity was altered no more than 25 per cent by the DNP[2]. A qualitatively different mechanism is thus associated with the inward movement of sodium during activity as compared with the extrusion of sodium during rest. Resting sodium outflux was also reduced in axons treated with potassium-free artificial sea water (20). This decrease, which was immediate and reversible, was neither the result of a permeability change nor of the slight increase in membrane potential which followed treatment of the axon with the low-potassium solution. It was suggested that a coupling exists between the active process of sodium extrusion and an active process of potassium uptake. A similar coupling for resting frog muscle was postulated by Keynes (21) as the outcome of an experiment in which the sodium outflux was reduced by removing the external potassium and was increased by raising the external potassium. The dependence of sodium movements on external potassium was also suggested by the experiments of Woodbury *et al.* (22) in which the resting potential of frog muscle bathed in potassium-free Ringer's solution was shown to decline, and glucose added to the muscle inhibited this decline. It should be added, however, that the rate of sodium outflux in frog muscle was not significantly altered by the addition of DNP, cyanide, or iodoacetate (18). This does not prove that sodium is not actively extruded from frog muscle, since it is not known that all energy sources were blocked. As a matter of fact the experiments of Woodbury *et al.* (22) indicated that, though the membrane potential of frog muscle bathed in potassium-free Ringer's solution showed an accelerated decrease under the influence of DNP, it was nevertheless able to restore itself even in the continued presence of DNP, as if a secondary, DNP-independent process had assumed control. The experiment which seems to be lacking is the one in which the sodium and potassium fluxes are measured in a muscle treated with DNP while bathed in potassium-free Ringer's solution.

Several reports appeared giving conditions under which the simple relation of the Nernst equation between membrane potential and potassium con-

centration was not obeyed. Using a microinjection technique, Grundfest *et al.* (23) introduced large quantities of potassium into the axoplasm of the squid giant axon and obtained little change in resting potential. Stephenson (24, 25) came to the conclusion that the membrane potential of muscle did not agree with the expectations of the Nernst equation in cases where rapid ion shifts were taking place.

The state of calcium in nerve fibers and the specific role which calcium ions play in nerve activity are still the major mysteries of this branch of neurophysiology. During the past year Rudenberg (26) cautiously suggested that some of the bound calcium of nerve may be bound to ribonucleic acid, and Soloway, Welsh & Solomon (27) measured the outflux of Ca^{45} from crayfish chela nerves and concluded that the data up to 200 min. were described by an equation with two exponential terms. A major contribution to the problem of the intracellular anion deficit of squid giant axons was made this year by Koechlin (28), who identified in axoplasm isethionic acid (2-hydroxyethane sulfonic acid) in quantity equal to the anion deficit of squid axoplasm. Of interest in connection with the ionic composition of muscle and nerve cells is the brief account by Caldwell (29) in which an intracellular pH glass microelectrode was described. The mean pH of *Carcinus* muscle fibers was given as 6.97 while a value of 6.8 was reported for the squid giant axon.

Some properties of the membrane.—The membrane of muscle fibers from different animals and under varying conditions was the subject of active and effective inquiry. The mean resting potential of intact muscle fibers of the white mouse was reported to be 99.8 mv. (30). A notable feature of this work was the finding of unusually high values of potential in many of the fibers, too high to be accounted for on the basis of the usual values for mammalian intracellular and extracellular potassium. Jenerick (31), focusing attention once more on the permeability of the muscle membrane to Na^+ and Cl^-, showed that the application of equations based on Goldman's constant field theory gave good agreement, except at zero external potassium, between expected and measured membrane potentials of frog sartorius muscle as a function of external potassium concentration. Jenerick's mean value for the specific membrane resistance was 2500 ohms/cm^2. In agreement with previous findings, an increase in external potassium was found to lower this resistance, the relation between log resistance and membrane potential being a linear one. Jenerick assumed that potassium moves across the membrane as a result of its electrochemical gradient. The work of del Castillo & Machne (32) is of interest in this connection, since they found an average Q_{10} of 1.35 for the specific membrane resistance of frog sartorius muscle, a value not greatly different from the corresponding Q_{10} for a 0.1 M KCl solution. The evidence, they concluded, provided no basis for participation by an active transport mechanism.

The exploration of cardiac tissue by means of intracellular electrodes was continued. Resting potentials were reported of 60.4 mv. for cat atrial fibers (33), of 85 mv. for dog atrial fibers, and of 85 mv. for dog papillary muscles

(34). Changes in external potassium for the cat atrial fibers produced changes in potential, the relation between potential and log potassium concentration being linear at values of potassium above 10 *mM* (33). The slope of this relation was only 62 per cent of the theoretical value for a potassium diffusion system.

A beginning was made in the study of smooth muscles by means of intracellular recording. Relatively high values of resting potential were reported for certain tissues, viz. 70 mv. [stomach of salamander (35)]; 40–75 mv. [guinea pig taenia coli (36)]; 64 mv. [iris (36)]. Woodbury & McIntyre (37) investigated the muscle fibers in the pregnant uterus and obtained unusually low values for membrane potential: 21 to 31 mv. (human), 32 to 52 mv. (rabbit), 27 to 66 mv. (guinea pig), and 29 mv. (cat). Several possible reasons for these low values were given, the one most favored being the occurrence of a heightened permeability to sodium. Oxytocin caused a reversal of the membrane potential in some of the uterine preparations, which was interpreted to be the result of an active increase in permeability to sodium.

An important paper on the properties of the membrane in crustacean muscle revealed some unexpected features (38). The mean resting potential in 144 fibers was 70 mv. Increase in external potassium caused depolarization, the relation between potential and log potassium concentration being linear over a limited range of concentrations. "Hysteresis" effects prevented a determination of the exact slope of the relation. The membrane resistance and capacitance were unusual since values of 100 ohms/cm.^{2} and 40 μf./cm.^{2} were found. Moreover, a fall in resistance occurred with rise in temperature (Q_{10} of 2.5) while the resting potential increased. The cause of the large membrane capacity is unknown though the authors suggested the presence, either of a structure with a large dielectric constant or, more likely, the occurrence of an excessively folded membrane. Martin (39) also called attention to the possible occurrence of a folded membrane in frog sartorius muscle. He found no significant change in conduction velocity in muscles whose lengths were altered over a range of 67 to 120 per cent of the resting length and he viewed this as the response of a folded membrane in which changes in length caused compensating changes in resistance, capacitance, and fiber diameter. The microelectrode technique was also applied to a study of the muscles in various insects (40). Resting potentials of the usual sign and ranging in values from 41 to 61 mv. were reported. Potassium produced a typical depolarization.

The membrane potentials of denervated muscles were examined. In one investigation (41) the resting potentials of the intact anterior tibial muscle of white mice were found to be unchanged (at about 100 mv.) for 24 to 48 hr. following denervation. Subsequently, the potentials decreased, rapidly at first, and then much more slowly, until at 50 days after denervation values of 77 mv. were obtained. The authors suggested that loss of potassium could have occurred after denervation but made no direct study of this possibility. Harris & Nicholls (42) did find that denervated frog sartorius muscle took up 63 to 85 per cent less K^{42} than normal muscle, a finding which they considered

to be a physiological effect rather than an atrophic change in surface area. In spite of this, however, Nicholls (43) obtained values of resting potential in frog muscles which were 85 mv. both for normal muscles and for denervated muscles. Denervation (23 to 169 days) resulted in an increase in length constant, a doubling of the specific resistance, and an increase in sensitivity to acetylcholine. The membrane capacity remained unchanged.

The resting potentials of frog sartorius muscle were found to be similar at the end-plate region and at nonneural portions of the fibers (44, 45). In addition, curare was ineffective in altering the end-plate resting potential. Another relevant finding was that of Kuffler & Vaughan Williams (46), who noted a difference in values of the resting potentials for the slow and the fast fibers in the iliofibularis muscle of the frog (Table I).

The Active Nerve and Muscle Fiber

The ionic hypothesis.—This hypothesis, so thoroughly reviewed in recent years (6, 47, 48), continues to play the dominant role in our thinking of excitation and conduction. Cole (6), in summarizing this hypothesis, added some valuable data from his own laboratory and pointed out that, though the formulations of this hypothesis involved the use of empirical methods, the ideas which emerged are both clear and useful. During the past year several additional investigations appeared in support of the ionic hypothesis. Using the giant axon of *Sepia officinalis*, Hodgkin & Huxley (49) demonstrated the occurrence of the expected effects of steady currents on potassium outflux, i.e., reduction by anodal currents and increase by cathodal currents. Moreover, the quantity of charge transferred out across the membrane was all accounted for on the basis of the potassium ion outflux. This experiment is relevant for, if the assumption is accepted that the steady outward current is analogous with the current which recharges the membrane during the recovery phase of the spike, then evidence of potassium current flow during the former process also applies to the spike. This experiment was not completely rigorous, for no information was obtained regarding the influx of potassium during the experimental period, but the authors considered this contribution to be small.

The ionic hypothesis is generally considered to apply to skeletal muscle (50). Desmedt (51) contributed some useful information and evidence for this. By soaking frog sartorius muscles in low-potassium Ringer's solution at 2° to 3°C., he allowed the intracellular sodium to increase and the intracellular potassium to fall. In such muscles though the resting potential increased immediately, the spike overshoot declined progressively (33 mv. to 13 mv.) as the intracellular sodium rose (17 to 68 mM/kg. fiber water). Except for low values of intracellular sodium the magnitude of the spike overshoot was that expected for a sodium diffusion potential. The rate of fall of the spike was similarly related to the intracellular potassium as expected for a potassium diffusion system. In this connection the observations of Grundfest *et al.* (52) are of interest since they were able to produce a highly localized reduc-

tion of spike height and a prolongation of spike duration by the injection of sodium into the squid giant axon. The occurrence of an overshoot in skeletal muscle was once more demonstrated by Furukawa (53), who obtained figures of 84.1 mv. and 117.4 mv. for the resting and action potentials of frog sartorius muscle at 18° to 24°C.

Action potentials from cardiac fibers were reported to have values of 65.2 mv. [cat atrial fibers (33)], and 105 mv. [dog atrial fibers and papillary muscles (34)]. Results concord with previous data on nerve and muscle except for measurements with cat atria. These had little overshoot, and in some cases the action potentials were less than the resting potentials. In no case did the action potential reach the theoretical value required for the sodium diffusion potential. The form of these cardiac action potential spikes was complex showing a discontinuity on the recovery phase. Stimulation of the vagus nerve resulted in a dramatic change of the dog atrial spike (34). This involved a reversible shortening of the recovery phase from 150 to 250 msec. down to 30 to 50 msec. This occurred in the absence of any effect on the magnitude of either the resting or action potential. Acetylcholine produced a similar effect but in addition, in some preparations, slight increases occurred in resting potential and in the maximum rate of rise of the action potential. None of these actions was observed in ventricular fibers or in papillary muscles. Burgen & Terroux (54) employed cat atrial fibers and found that acetylcholine consistently increased the resting potential and hastened repolarization. To explain their results of vagal stimulation and of acetylcholine, Hoffman & Suckling (34) postulated the existence in cardiac muscle of a mechanism which actively delays repolarization. Acetylcholine was visualized as inactivating this mechanism, thus hastening repolarization. Dog ventricular tissue did not respond in the same way because of the lack of cholinergic endings which, it was postulated, are the sites of acetylcholine action.

The ionic hypothesis assumes that activity is associated with a dual change in permeability. In accordance with this expectation, Grundfest *et al.* (55) found in squid giant axon a dual dependence of the activity impedance change on both the sodium and potassium concentrations of the external solution. Fatt & Katz (44), it will be recalled, noted in frog muscle a dual change in resistance associated with the rising and falling phases of the action potential spike. This dual effect was strikingly demonstrated in a recent experiment by del Castillo & Katz (56). It should be noted, incidentally, that in addition to the spike impedance changes there have been observed recently (57) after-impedance changes of a low magnitude. These consisted (*a*) of an initial decrease in conductance below the resting level, and (*b*) of a sequence of changes associated with the actions of cevadine and veratridine. Schoepfle & Grant (58) analyzed the distortion of the electrotonic potential as the result of treating desheathed frog nerves with sodium-free solutions. They suggested that a change in conductance of the nerve fibers to potassium was the basis for the effects which were observed. Shanes (17) interpreted his results on the

low temperature modification of the potassium outflux of nerve fibers during activity as fulfilling the expectations of the ionic hypothesis.

The problem of whether cations, other than sodium, can replace sodium in the reactions of nerve and muscle fibers has occasionally arisen. There is general agreement that lithium can replace sodium, but these ions are neither normally present in sufficient concentration nor are they physiologically suitable. Lorente do Nó (59) made a case for certain quaternary ammonium ions in the activity of the B fibers of the frog sciatic nerve but this was not confirmed (60) for the case of tetraethylammonium. The inability of TEA to substitute for sodium in the case of *Carcinus* axons was also adequately demonstrated (61). The situation is different, and quite puzzling, for the case of crustacean muscle fibers (38). In these fibers not only was it proved that activity persisted in the absence of sodium when choline and TEA[2] were provided, but that the action potentials obtained in the presence of these organic ions were of greater magnitude, greater rate of rise, and longer duration. In addition, muscle contractions occurred and were more powerful and prolonged with choline or TEA. In all these reactions TEA was discovered to be more effective than choline. These curious results raise the problem of the origin of the excitatory process under these conditions. Data are not yet available to decide whether or not cations other than sodium, or else anions, can function in the transfer of charges across the membrane in the absence of sodium.

According to Fatt & Katz (44) the reactions at the end-plate of frog muscle cannot be explained in terms of the ionic hypothesis. Instead of a selective change in permeability they proposed the idea of a generalized increase in permeability, i.e., a short circuit of the muscle fiber. Nastuk (45), on the other hand, found no reason to postulate a different mechanism at the end-plate. These statements will be amplified in a later section.

Properties of different nerve fibers.—The past year's work resulted in a number of reports which made comparisons of properties in nerve fibers from various portions of the nervous system and from various animals.

Several studies were concerned with the central fibers. The nerve fibers in the cat optic nerve were studied using mainly antidromic stimulation in the optic tracts (62). Each optic nerve was found to contain about 120,000 myelinated fibers in the size range (axonal diameter) of 1 to 8.5 μ. Histologically, a segregation of fibers was noted with the smaller fibers (1 to 2 μ) located uppermost in the tract. Records of electrical responses revealed two distinct waves the relative size of which varied with the locus of stimulation in the tract. Except for the duration of the supernormal period, the optic nerve fibers were considered to be similar in properties to mammalian peripheral A fibers. The authors found no evidence in support of the idea of a triple conducting pathway in the visual system as postulated by Chang & Kaada (63). Bishop, Jeremy & Lance (64) carried out a similar investigation on the fibers of the cat pyramidal tract. They recorded electrograms with

two distinct elevations which they considered to be the result of activity in two separate groups of fibers which conducted at velocities of 35 to 40 m.p.s. and 12 to 16 m.p.s. The more slowly conducting fibers were found to be more readily susceptible to 1 per cent cocaine and to anoxia. Several properties of these two fiber groups suggested a similarity to peripheral A fibers. In another investigation (65) the course of these two groups was traced down the cord but no functional correlations were made. Using frog spinal cord, Holmgren (66) confirmed the occurrence of a reduction in conduction velocity in fibers traveling in the dorsal tracts (20 m.p.s. to 2.2 m.p.s.). Decreases in velocity were noted at the point of entry of the afferent fibers into the cord and at higher levels in passage up the cord. These decreases were believed to be associated with reductions in fiber diameter at the point of entry where branching occurs and higher up in the cord where collaterals are assumed to be given off.

Isolated funiculi from the cat spinal cord were utilized in a study of the properties of the cord fibers (67). The column compound action potential was observed to be simple in form, decreasing in both height and area with increasing conduction distance. No evidence was recorded for fibers conducting at a velocity less than 15 m.p.s. in dorsal columns or less than 50 m.p.s. in ventral columns. A maximum velocity of 118 m.p.s. was measured in fibers from ventral columns. Though some of the properties such as spike duration, rise time, and conduction velocity were similar in these fibers and in peripheral A fibers, there appeared to be a number of differences such as in oxygen consumption, dependence on CO_2, after-potentials, and capacity for spontaneous firing. The authors were explicit in pointing out that the funiculi are complex structures and the possibility exists that the nonneural elements of the funiculi could have been involved in the determination of some of the characteristics which were observed. A direct examination of single myelinated fibers in the dorsal funiculus of the frog spinal cord was made by Tasaki (68) using microelectrodes. He obtained evidence for the occurrence of closely spaced (200 to 400 μ) "sensitive spots" which he interpreted to be Ranvier nodes. Tasaki supported the idea of saltatory conduction for fibers of the central nervous system.

Properties of spinal motoneurones.—Brock *et al.* (69) accomplished the difficult task of intracellular recording from single spinal motoneurones. The resting potential (69 mv.) was considered to be of the same order of magnitude as that of peripheral nerve fibers so that no steady potential difference between soma and axon was thought to exist. The action potentials had overshoots of about 25 mv. and the spike duration was of the order of one msec., longer than the comparable figure for mammalian nerve fibers. Negative and positive after-potentials were present, the latter being relatively larger than in mammalian A fibers. Araki *et al.* (70) made a similar study on toad spinal motoneurones. There were considerable variations in values of resting and action potentials, and overshoot was observed in some cells but not in all. Maximum spikes of 70 mv. were obtained in cells with resting potentials of 50

mv. In other respects, however, the properties of the toad motoneurones were similar to those of the cat as described by Brock *et al.* (69). In another study (71) the responses of motoneurones to currents applied through a second intracellular electrode were found to be similar to the well-known effects of currents on axons. Nonpropagated depolarizations, multiple responses, facilitation and block were all observed, the effects being related to the direction and strength of the applied current. The responses of frog spinal motoneurones to weak direct current applied antidromically through ventral root fibers were examined by Alanis (72). Such current was considered to spread electrotonically and to affect only the neurones of the root or root filament to which the current was applied. The responses to cathodal current consisted of slowly adapting (relative to skin receptors) repetitive discharges whose frequency varied with stimulus strength and with the distance of the stimulating electrodes from the cord. Facilitation of afferent stimulation was noted and this was assumed to occur (*a*) in the motoneurones and (*b*) in the interneurones connected with the motoneurones.

Conduction from axon to soma.—Brock *et al.* (73) published electrograms, obtained by intracellular recording of spinal motoneurones following antidromic stimulation, which, instead of a simple spike form, showed evidence of discontinuity. The interpretation by the authors, with which not everyone will agree, was that the microelectrode recorded not only the SD spike (up to 100 mv.) which was the response of the soma-dendrite region, but also a smaller NM spike (30 to 40 mv.) which represented activity in the nonmedullated portion of the axon and a still smaller M spike (1 mv.) associated with activity of the medullated segment of the axon. Experiments were described in which the SD and NM spikes were independently and successively abolished. The interactions of these three components were discussed and it was concluded that, in antidromic conduction into the motoneurone, blocks can occur at two functionally critical regions of the neurone pathway: (*a*) the axon-soma junction and (*b*) the medullated-nonmedullated junction. Electrical responses following antidromic stimulation were believed to be recorded from inside the large Mauthner cells in the medulla of the catfish (74). Resting potentials up to 60 mv. were measured and the action potentials never showed the presence of overshoot. Moreover, the action potentials consisted of a spike-like component, which was interpreted as a cell-body response, followed by a slow potential which was interpreted to be a dendritic action. The author stressed the possibility that injury may sometimes modify the responses obtained with intracellular electrodes.

Peripheral nerve fibers.—In a technically careful investigation Hodes (75) pointed out that the square root relationship between conduction velocity and fiber diameter did not fit his data for squid giant axon. Instead, velocity and diameter were related in a linear manner as for the case of vertebrate myelinated fibers. Using a method which involved identification of impulses with specific receptor activity, Paintal (76) measured the conduction velocities of vagal afferent fibers whose receptors were pulmonary stretch receptors,

atrial receptors, chemoreceptors, depressor receptors, and receptors stimulated by phenyl diguanide. The conduction velocities ranged from 2 to 61 m.p.s. with considerable overlap between the fibers of different types. A comparison of the compound action potential of the cat vagus with the conducduction velocity data suggested that some previous ideas regarding the fiber types contributing to the B elevation of the vagus electrogram may have to be modified, viz. that the contribution by visceral afferent fibers has been underestimated. Because of the considerable overlap in properties, the author cautioned against the supposed physiological selectivity produced by stimulation or by fiber block experiments in the case of the vagus nerve. A study (77) of the characteristics of afferent fibers with terminations in the tooth pulp of the cat revealed these fibers to be myelinated with a size range from 1 to 7 μ, conduction velocities from 30 to 45 m.p.s., and strength-duration curves resembling those of the saphenous A-gamma and A-delta groups.

In recent years nerve fibers have been shown to be capable of adaptation to temperature. Chatfield *et al.* (78) first reported that the minimum critical temperature at which isolated tibial nerves ceased activity was lower (3.4°C. as compared with 9.0°C.) in nerves from a hibernating mammal (golden hamster) than in nerves from the nonhibernating rat. An example of acquired resistance to cold was reported (79) for herring gull nerves in which the metatarsal portions of the peroneal nerves, located in the unfeathered lower part of the legs, were compared, in their responses to cold, to the proximal tibial portions of the same nerves. In nerves from cold-adapted animals the metatarsal peroneal retained its ability to conduct at significantly lower temperatures than did the tibial peroneal from the same animals. This resistance to cold was less in nerves from warm-adapted animals and least in nerves from heat-adapted animals. In addition, the ventral caudal nerve of the albino rat was also shown to possess a greater resistance to cold block than the tibial nerve from the same animal (80). These results suggest that nerve cells have interesting potentialities in the study of phenomena associated with thermal adaptation.

The functionally different motor nerve fibers of crustacea have in the past been claimed to possess different properties (8). The positive identification of different properties is fraught with difficulties, however, since, in isolation, and with frequent stimulation, these axons run down and change in properties. Wright *et al.* (81, 82) undertook the heroic task of analyzing three types of fibers in the crayfish claw and the lobster walking leg. Although the data showed considerable dispersion and overlap, the authors concluded that these three fibers are functionally different. The fast closer, the largest of the three, was considered to be a fiber of high threshold, long refractory period, short response time, small accommodation time constant, and with limited ability to respond repetitively to direct current stimulation. The slow closer, intermediate in size, was intermediate in threshold, response time, ability to accommodate, and ability to fire repetitively. It was a fiber with the shortest refractory period. The opener fiber, the smallest of the three, had the lowest

threshold, the most rapid response time, and the longest accommodation time constant. The refractory period was not greatly different from that of the fast closer. This fiber was easily thrown into a long lasting state of repetitive firing. From a comparison of slow closer fibers which fired repetitively and those which did not, and from studies of fibers which, with continued activity, lost the ability to fire repetitively while increasing the ability to accommodate, the authors concluded that repetitive firing and low ability to accommodate are related. Katz (83) almost twenty years ago pointed out the relationship between the accommodation time constant and the ability to fire repetitively. The alteration in properties with continued stimulation may be the result of potassium loss and accumulation because poorly accommodating, repetitively firing fibers were quickly and reversibly converted to highly accommodating, nonrepetitive fibers after exposure to a solution with two to five times the normal concentration of KCl (84).

A preliminary report (85) on conduction in embryonic nerves revealed that propagated action potentials could be elicited in sciatic nerves of 9th day chick embryos before the histological appearance of any myelin sheath. Conduction velocity increased from 15 to 20 cm.p.s. at the 10th day of incubation to 4 m.p.s. at hatching.

The problem of the sheath.—There appears to be no lack of evidence for the view that the epineurium (referred to as perineurium by some) is a significant diffusion barrier for substances entering or leaving a nerve trunk. In addition to several additional reports on sheath effects (86 to 89) new morphological data appeared showing the presence of cellular components in the sheath which must be traversed before substances applied externally can affect the nerve fibers (86, 90, 91). The criticism that desheathing a nerve results in alterations in properties of the nerve fibers, thus accounting for the more rapid action of substances in the case of desheathed nerves, cannot be applied to the experiment (89) in which various substances introduced into the nerve via the circulatory system were shown to act as rapidly as the same substances applied externally to desheathed trunks. The most direct demonstration of the diffusion properties of the nerve sheath is that of Shanes (92) in which sacs were constructed of isolated sheaths of the bullfrog sciatic nerve and in which the rate of movement of radioactive sodium out of these sacs was compared and found to be similar to the rate out of the intact nerve. This reviewer expresses the hope that the controversy of the sheath is a matter for history and will no longer arise to plague neurophysiology.

Acetylcholine.—The role of acetylcholine in conduction continues to generate lively discussion. Wolfgram (93) contributed some useful data which cannot be easily ignored. Utilizing biochemical methods, Wolfgram was able to show that, whereas homogenates of cattle dorsal roots synthesized insignificant quantities of acetylcholine, similar preparations from the ventral roots formed 82 to 124 μg. of this substance per 576 mg. of fresh tissue in 8 hr. The dorsal roots were therefore considered to lack choline acetylase. In contrast to this, the two roots were found to have about the same amount of true and

pseudocholinesterase. In terms of a universal acetylcholine hypothesis for nerve fibers this appears to be an anomalous situation. The failure of the optic nerve to synthesize significant quantities of acetylcholine was also mentioned by Hebb (94, 95), who also called attention to her failure to demonstrate true cholinesterase in this nerve and to her demonstration that, though pseudocholinesterase is present in the optic nerve, it is located in the glial cells and septa and not in the nerve fibers. The advocates of the acetylcholine theory have consistently supported the thesis that peripheral nerve fibers fail to respond to this substance because of the presence of barriers to its entrance (96). Yet now one reads (97) that acetylcholine applied externally to certain nerve fibers is able to produce a conduction block. It has also been claimed that acetylcholine can have excitatory actions on the fine terminals of certain afferent nerve fibers. Douglas & Gray (98) interpreted their experiments as indicating an acetylcholine excitation of the sensory nerve terminals in the skin of the cat. For reasons that are presented later in this review this excitation was not interpreted as evidence in favor of a cholinergic mechanism. The fact that acetylcholine may be capable of exciting certain neuronal terminals is no proof that it is capable of exciting all neuronal surfaces. In addition to the hypothesis of a barrier to entry there is also the hypothesis of specialization of neuronal surfaces. In this connection the suggestion of Fatt & Katz (99) is worth recalling. According to Fatt & Katz the motor nerve endings are functionally specialized so that activity leads to the outflux of acetylcholine ions in exchange for Na^+, a process which is analogous to the Na^+-K^+ exchange of other portions of the nerve fiber.

The nerve-blocking action of certain anticholinesterases has been interpreted as being the result of interference with cholinesterase activity (100), even though several groups of investigators were able to dissociate nerve block from enzyme inactivation (101, 102). Most recently, Holaday *et al.* (103) pointed out that ganglionic transmission was modified by doses of DFP^2 which had no significant influence on preganglionic conduction. These investigators concluded, as others had done before, that conduction block, when it occurs with DFP, involves effects other than anticholinesterase effects.

Space limitations forbid the discussion of a number of publications in which the actions were described of various substances on peripheral nerve fibers (104 to 116).

Transmission at Junctions

Neuromuscular junctions.—An important recent advance involved the intracellular recording of the electrical events at the end-plate (44, 45). Such recordings revealed a number of characteristic properties of the end-plate. It was shown, for example, that end-plates in frog muscles give rise to small, spontaneous, and random electrical responses (miniature end-plate potentials) presumably resulting from localized, spontaneous and random unit discharges of acetylcholine from the motor nerve endings (117, 118). These min-

iature end-plate potentials were reduced in amplitude by curare and increased in size and duration by cholinesterase inhibitors (117); they were reduced in number by excess magnesium and by calcium lack (118). Each one of these unit discharges was considered to be an all-or-none event subject to independent statistical fluctuations (119), although the chances of the occurrence of a discharge were considered to be subject to variation. The miniature end-plate potentials were employed by del Castillo & Katz (120) in an experiment which once again called attention to the inability of local circuits to spread across the myoneural junction. These investigators demonstrated that electrotonic spread did in fact reach the motor nerve endings, so that the failure to cross the junction was a failure of transmission by local circuit rather than a result of attenuation at the fine nerve endings.

The action potentials on and off the end-plates were thoroughly described by two groups of investigators (44, 45) who agreed that differences exist in these responses as recorded intracellularly from these two regions of the muscle fiber. The end-plate response was described as a "step-peak-hump" complex. Off the end-plate the action potential was higher in amplitude, greater in overshoot, lacked the hump, and recovered at a faster rate. Fatt & Katz (44) concluded that these differences were not attributable to special properties of the end-plate membrane, since direct electrical excitation of the end-plate by means of an internal stimulating electrode gave responses like those off the end-plate. but were the result of transmitter action. According to Fatt & Katz acetylcholine causes a generalized increase in permeability of the end-plate, i.e., a short-circuit. One expectation of this short-circuit theory, i.e., that stimulation through a motor nerve fiber should result in a greater breakdown of membrane resistance than direct stimulation of the muscle fiber, was fulfilled in a recent experiment by del Castillo & Katz (56). Nastuk's interpretation of the events at the end-plate is quite different (45, 121). Nastuk found that the depolarizing action of acetylcholine was decreased by a factor of 14 when NaCl was removed from the external fluid. The residual depolarization in the absence of sodium was considered to be the result of entrance of acetylcholine ions. Nastuk's thesis is that acetylcholine brings about a selective increase in permeability to sodium ions which cross the membrane, thus decreasing the membrane potential and resulting in the overshoot. The differences in responses on and off the end-plate are assumed by Nastuk to be attributable to (*a*) a special relation between acetylcholine action and the level of the end-plate potential and (*b*) the persistence at the end-plate of the transmitter. Fatt & Katz (99) have expressed a somewhat different point of view with respect to the role of sodium at myoneural junctions. According to these workers, sodium, like calcium, is required for the liberation of acetylcholine at the nerve endings and is also required in order to maintain an adequate sensitivity of the end-plate to acetylcholine.

Neuromuscular systems: vertebrates.—The excellent work of Kuffler and his group (46, 122, 123) on the small-nerve system of the frog was brought to

a definitive stage in experiments in which the slow and fast systems were shown to utilize separate nerve and muscle fibers. The properties of these two systems were carefully analyzed, and some important deductions were made concerning differences in innervation. Table I lists the outstanding characteristics of the twitch and small-nerve systems. The action potentials of the slow fibers (called small-nerve junctional potentials) were composite and, with increasing stimulation strength, were shown, by intracellular recording, to consist of successive steps. These results were interpreted as indicat-

TABLE I

NEUROMUSCULAR SYSTEMS OF THE FROG*

	Twitch System	Small-Nerve System
Approximate size of nerve fibers	12 μ	5 μ
Conduction velocity of nerve fibers	8–40 m.p.s.	2–8 m.p.s.
Resting potentials of muscle fibers	Distribution peak at 95 mv.	Distribution peak at 60 mv.
Action potentials of muscle fibers	110–130 mv.; overshoot present; fast, propagated, all-or-none response	8–10 mv.; no overshoot; a slow, local, graded response; large, positive after-potentials
Nature of contraction	Rapid; responds to single stimulus; relaxes quickly	Slow; local, repetitive stimulation required; relaxes slowly
Response to acetylcholine and to potassium	Transient tension	Maintained tension

* Data selected from the work of Kuffler *et al.* (46, 122, 123).

ing a multiple innervation by several small nerve fibers of one slow muscle fiber over its entire length. In this way synchronized activation of many small-nerve junctions overcomes the shortcomings of nonconducted responses and also provides a mechanism through which graded contractions may be evoked through nervous control. Kuffler (123) pointed out that multiple innervation of twitch muscle fibers also occurs, but, even so, the density of innervation is below that of the slow muscle fibers. The difference in reaction of the two muscle systems to acetylcholine and to potassium serves to clarify the apparent discrepancy observed when acetylcholine is applied to an endplate causing a transient response and when a whole frog muscle is treated with this drug, causing a maintained contraction.

Neuromuscular systems: invertebrates.—Intracellular recording of activity in crustacean and insect muscles has been accomplished by several groups of investigators (124, 125). The results were not altogether lucid, in so far as this reviewer is concerned, but it is recognized that these muscle fibers are often easily subject to injury, the effects of which are not readily apparent. Fatt & Katz (124) examined the distribution in crustacean muscle fibers of the local depolarization (e.p.p.) produced in response to nerve stimulation. They found, unlike the e.p.p.[2] of vertebrate muscle, a uniform distribution, with only minor variations over the muscle fiber. This was interpreted to be the result of a widespread distribution of nerve endings and not the result of electrotonic spread. This system is thus analogous to the frog small-nerve system and permits powerful contractions to occur in the absence of conducted responses. Fibers of the flexor tibialis muscle of the locust were investigated by means of intracellular electrodes and a temperature analysis revealed the presence of both an e.p.p. and an active membrane response (125). The action potentials were highly variable in magnitude but fibers in good condition revealed overshoots as high as 20 mv. Contractions were observed in the presence of only the e.p.p. The possibility was suggested that the e.p.p. in locust muscle fibers was the result of a short-circuit of the membrane as was postulated for frog end-plates by Fatt & Katz (44).

With the perfection of the technique of intracellular recording it should be possible to make accurate analysis of the separate effects of stimulating the individual axons which mediate different responses in the same crustacean or insect muscle fiber.[3] Furshpan & Wiersma (126) reported in a preliminary communication that stimulation of fast and of slow axons produced different electrical responses in the muscle fibers. Slow and fast nerve fibers are known for the extensor tibialis muscle of the locust (127). Using this preparation, Hoyle (128) found that stimulation of the fast fiber caused an e.p.p. and an action potential with an overshoot of 10 to 20 mv. This response was much the same whether recorded from different muscle fibers or from different spots in the same fiber. The responses evoked as the result of slow fiber stimulation were much more variable and depended on the rate of stimulation, the position of the intracellular electrode, and other factors. A paper of considerable importance was one by Fatt & Katz (129) in which the crustacean e.p.p. was recorded with and without stimulation of the inhibitory axon. Confirming previous findings, inhibitory impulses were found to depress the height of the e.p.p. and to accelerate its decay, the magnitude of the effect depending on the time relations of the inhibitory and excitatory shocks. Analysis of the inhibitory action revealed that, though the inhibitory impulses had no effect, or only occasional effects, on the resting potential of the muscle fibers, these impulses were able, however, to cause significant swings of potential in a membrane whose resting potential was previously

[3] A paper (163) which was received too late to be incorporated in the text suggested that fast and slow fiber activity in the flexor tibiae muscle of the cockroach occur, not in the same, but in different muscle fibers. If true, this suggests the occurrence of a similarity in the neuromuscular systems of insects and frog.

displaced by applied currents. With the membrane potential reduced below some equilibrium level (near the resting level) inhibitory impulses evoked a transient increase in potential. The opposite effect was observed when the membrane was placed in a hyperpolarized state. The effect of inhibitory impulses on the membrane potential was considered to be a by-product rather than a cause of the depression of the e.p.p. which followed stimulation of the inhibitory axon. In general terms, inhibition was looked upon as a competitive action between an inhibitory transmitter (I) and an excitatory transmitter (E) for a receptor surface with which both I and E can combine.

Synaptic junctions.—An elegant series of studies appeared on transmission in the dorsal nucleus of the cat lateral geniculate body (130, 131). Utilizing extracellular microelectrodes, the authors were able to record and to distinguish electrical responses in the presynaptic optic tract fibers (t_1), the postsynaptic fibers of the optic radiation (r_1), and the synaptic potential. Stimulation of the larger fibers of the contralateral optic nerve was employed to elicit these responses. Differentiation of these various components was neatly accomplished through the use of axphyxia, pentobarbital anesthesia, and repetitive stimulation. The principal conclusions were that the presynaptic impulses are propagated to the tips of the presynaptic axon terminals, that a true synaptic delay of about 0.4 msec. occurs, that conduction along dendrites probably does not take place, that the synaptic potential represents a depolarization of the postsynaptic dendrite-cell-body complex, and that current flow associated with the synaptic potential is involved in the excitation of the postsynaptic axon. A similar opinion as to the site of occurrence of the synaptic potential is held by Brock, Coombs & Eccles (69, 132), who demonstrated in spinal motoneurones that afferent volleys produced graded depolarizations which, when of sufficient magnitude, generated a spike. The analogy of the synaptic potential with the end-plate potential is suggested, and the term postsynaptic potential is considered to be more accurately descriptive. Bishop, Jeremy & McLeod (133) also made a study of the repetitive firing which appeared in recordings from the lateral geniculate body in response to a single stimulus to the optic nerve. These discharges were considered to originate in postsynaptic fibers and to be the result of activity in simple reverberating circuits involving short axon internuncial neurones. It should be pointed out, incidentally, that an attempt has already been made, though unsuccessful, to record intracellular activity in neurones of the cat lateral geniculate body (74).

Inhibition.—The knotty problem of central inhibition is receiving attention as the result of some energetic publications from Australia. The start of this output was the observation (69, 132) that direct inhibition of the cat spinal motoneurones caused a hyperpolarization (called the inhibitory postsynaptic potential or IPSP) of the motoneurone membrane. Unable to explain this on the basis of the effects of current flow, the authors resorted to the idea of a chemical transmitter of inhibitory action. It was next shown (134, 135) that strychnine in subconvulsive concentrations was able to de-

press the inhibitory action and two possible mechanisms for the strychnine effect were suggested: (*a*) strychnine competes with the hypothetical transmitter, or (*b*) strychnine depresses the IPSP.[2] A possible mechanism for the production of the IPSP was next suggested (136) by the observation that this potential declined and eventually reversed in sign when microelectrodes containing 3*M* KCl were employed but was unchanged when using microelectrodes filled with sulphate or phosphate. The idea was conceived that the inhibitory transmitter leads to a specific increase in permeability to Cl^- which, as a result of the electrochemical gradient, moves in, thus transferring negative charges across the membrane and leading to a hyperpolarization. In accord with this hypothesis, changes in resting potential produced by applied currents caused the IPSP to change, a reversal in sign occurring at a value which, according to the Cl^- hypothesis, would be the equilibrium potential for Cl^-. The authors of this idea outstripped their experimental evidence, even suggesting the existence of a chloride pump to eject the extra Cl^- taken up during inhibition. In another communication (137) it was observed that hyperpolarization of spinal motoneurones also occurred when antidromic impulses were fired into adjacent motor fibers, a procedure which is known to depress excitability of the motoneurones. It was also observed that a microelectrode suitably placed in the ventral horn could record a repetitive discharge in response to a single antidromic volley. The origin of this repetitive discharge was postulated to be a synapse between motor axon collaterals and an interneurone which, in turn, connected with a neighboring motoneurone. From the effects of acetylcholine-blocking drugs and of anticholinesterases it was concluded that the collateral-interneurone synapse is cholinergic. The possibility that cholinergic systems occur in the spinal cord has of course been suggested before. Feldberg *et al.* (138) utilized the procedure of close arterial injection and found that acetylcholine increased the spontaneous electrical activity and the polysynaptic reflex discharge as recorded from a C-1 ventral rootlet. Physostigmine and neostigmine were reported to prolong the responses to acetylcholine and to reflex stimulation. From the nature of the responses the authors believed that interneurones were primarily involved. A paper by Taverner (139) reported that physostigmine, injected intra-aortically, was able to increase the amplitude of both monosynaptic and polysynaptic reflexes and that atropine depressed these effects of eserine. On the basis of the central latency of the IPSP, Eccles *et al.* (140) concluded that an interneurone is also interpolated in the so-called direct inhibitory pathway of the cord. From microelectrode explorations of the cord it was postulated that this pathway involves an interneurone which makes synaptic connections in the intermediate nucleus with collaterals from the afferent fibers.

Cholinergic Systems

Any thesis which attempts to demonstrate a role for acetylcholine in junctional transmission should satisfy four essential requirements. These are:

(*a*) the appearance of acetylcholine as the result of physiological activity, (*b*) the production by acetylcholine of responses reasonably similar to the physiological responses, (*c*) the occurrence at the junction of the enzyme systems (choline acetylase and true cholinesterase) involved in the biosynthesis and hydrolysis of this ester, and (*d*) alteration of the process of transmission by any drug or agent which alters the release, destruction, or action of the acetycholine. It is desirable, of course, that all four of these criteria be satisfied before a clear case can be said to exist for acetylcholine. Yet it is surprising how many claims for cholinergic mechanisms exist in the literature on the basis of quite inadequate evidence. Many investigators, for example, employ cholinesterase inhibitors or drugs which compete with acetylcholine in the analysis of events which take place at junctions. The present reviewer is of the opinion that, though the judicious use of such drugs has been, and will continue to be, of value in elucidating physiological processes, too often, however, the casual use of such drugs leads to overinterpretations which hardly seem warranted. These drugs often have several actions which depend upon concentration of drug, conditions at the site of action, and other factors. It is not correct, for example, to assume that the effects of cholinesterase inhibitors are always attributable to the inactivation of cholinesterase. There are several examples in the recent literature which suggest that these agents exert effects other than through their attack on this enzyme. Recently, Holton (141) pointed out that physostigmine, neostigmine, and DFP were able to reduce the vasodilatation in response to antidromic stimulation without showing any phase of potentiation. Holaday *et al.* (103) also called attention to the depressant effects of DFP on ganglionic transmission by doses higher than those required for complete inactivation of cholinesterase. A dissociation of pharmacological actions and anticholinesterase activity was also noted by McNamara *et al.* (142) for DFP and TEPP.[2]

The demonstration of excitatory effects by applied acetylcholine does not necessarily constitute evidence for a cholinergic mechanism. Douglas & Gray (98), for example, obtained evidence of excitation in skin nerve terminals by acetylcholine, but hexamethonium or *d*-tubocurarine was able to prevent these excitatory actions without altering the responses to touch or to KCl. It is doubtful, therefore, whether this reaction to acetylcholine is of physiological significance. Diamond's acetylcholine responses (143) with the pressor receptor system of the cat carotid sinus appear to fall in the same category, and doubt was also expressed as to whether chemical transmission is involved in the events associated with excitation in the cat Pacinian corpuscle (144).

Sympathetic ganglia and motor end-plates.—Paton & Perry (145) filled in a missing piece of evidence for cholinergic transmission in sympathetic ganglia by the demonstration that acetylcholine in small doses was able to produce a transient depolarization of the superior cervical ganglion, an effect which was potentiated by physostigmine. In large doses acetycholine caused, not only depolarization, but also a reduction of the synchronized spike dis-

charge. An examination of the responses to several drugs revealed two types of blocking action: (*a*) block by depolarization (acetylcholine, nicotine, tetramethylammonium); and (*b*) block by competition with acetylcholine (*d*-tubocurarine, pentamethonium, hexamethonium, tetraethylammonium, and decamethonium in large doses). This classification was also applied to the motor end-plate except for decamethonium which, at the latter junction, acted as a depolarizing agent.

The development of histochemical methods for cholinesterases has led to the cytological localization of these enzymes. The cholinesterases of myoneural junctions have been especially beautifully located by these techniques (146, 147). Denz (147) demonstrated that both specific and nonspecific cholinesterases are found at these junctions with the former enzyme as the chief one. The superior cervical ganglion is also known to contain both true and pseudocholinesterase (148), and the action of DFP in facilitating transmission through this ganglion was interpreted to be the result of inactivating the true enzyme (149). Chessick, however, issued a warning (150) against the histochemical classification of cholinesterase into definite biochemical types. His findings demonstrated considerable overlap in properties the degree of which varied according to tissue and according to species. Denervation has been found to result in a decrease of the true cholinesterase content of the innervated structure, and this has been interpreted to be the cause of the hypersensitivity to acetylcholine. Burn & Philpot (151) noted, for example, that removal of the superior cervical ganglion in the cat led to a fall of the cholinesterase of the nictitating membrane. This experiment, incidentally, fits in with a suggestion (152) that some of the sympathetic fibers to the nictitating membrane may be cholinergic.

The actions of a number of ions at synapses and at motor end-plates have been explained in terms of interferences at specific points in the cholinergic chain of reactions. Some ideas about the role of sodium were discussed in a previous section of this review. The ions of calcium and magnesium are currently of great interest in respect to the mechanism of their action at these junctions. Hutter & Kostial (153) determined that $MgCl_2$ in concentrations (15 to 25 mM) which blocked transmission in the cat superior cervical ganglion also reduced the output of acetylcholine in response to preganglionic excitation. Moreover, these effects of magnesium were reversed by calcium in concentrations (4 to 10 mM) which, without magnesium, were shown to increase the output of acetylcholine [see also del Castillo & Stark (154)]. The responses of frog sartorius muscle to magnesium and calcium were carefully studied by del Castillo & Engbaek (155), who found that magnesium has a number of actions, but the main one, from a quantitative point of view, is the decrease in amount of acetylcholine liberated at the junction. Their principal findings were the following: (*a*) magnesium in concentrations as low as 5 to 10 mM blocked transmission and reduced the e.p.p., these effects being reversed by calcium at concentrations of 1 to 4 mM; (*b*) magnesium decreased the end-plate sensitivity to acetylcholine in noncurarized muscle,

but increased this sensitivity in curarized muscle, while calcium did not antagonize the effect on noncurarized muscle; (*c*) magnesium at a level of 15 m*M* increased the activity of cholinesterase of muscle homogenates, but this action was unaffected by calcium; (*d*) the threshold for action potential generation was increased from about 34.5 mv. to 53.7 mv. by magnesium (15 m*M*) but this, too, was independent of calcium; (*e*) the resting potential was not altered by concentrations of magnesium up to 15 m*M*. Of these actions, those which involved a calcium-magnesium antagonism were considered to be concerned with the mechanism of liberation of acetylcholine. A calcium-magnesium antagonism was also observed to occur in the mechanism responsible for the production of the miniature e.p.p. (118). The levels of concentration of calcium and magnesium required for modifying the miniature e.p.p. discharge were such as to suggest possible physiological implications. The suggestion was made (156) that calcium may play a similar role in the release of the transmitter during vagal inhibition of the anuran heart.

The results of axotomy on transmission through a sympathetic ganglion have also been explored. Transmission through such a ganglion was shown to fail as the result of section of the postganglionic fibers (157, 158). This failure was interpreted to be the result, not of a failure of liberation of the transmitter, but of a loss in sensitivity to acetylcholine on the part of the postsynaptic cells (158). The cause of this loss in sensitivity is unknown, although claims have been made (159) of a decrease of true cholinesterase in axotomized ganglia. Changes in transmission through monosynaptic reflex pathways of the cat spinal cord following section of the ventral roots have also been described (160).

Parasympathetic synapses.—The morphology of most parasympathetic ganglia and endings has presented a technical barrier to the separate analysis of processes at parasympathetic synapses and at postganglionic neuroeffector junctions. Perry & Talesnik (161) have made such an analysis with the cat ciliary ganglion. Electrical responses recorded from the body of the ganglion and the postganglionic ciliary nerve while stimulating the oculomotor nerve consisted of two fast components, the second smaller than the first, and a slow, positive ganglion potential. Arterial injections of large doses of acetylcholine depolarized the ganglion, decreased the electrical response to stimulation, and altered the character of the response by shortening the time to maximum of the positive phase. Similar effects followed the injection of nicotine. An injection of 20 μg. of acetylcholine was able to potentiate the postganglionic spikes evoked by submaximal preganglionic stimulation. No spontaneous discharges in postganglionic fibers were noted in response to acetylcholine injection. In spite of the fact that the release of acetylcholine following presynaptic excitation has not yet been demonstrated for the ciliary ganglion, the authors considered the evidence sufficient to support the concept of the cholinergic nature of these junctions. Perry & Talesnik also noted that hexamethonium was capable of reducing the electrical response to stimulation without depolarizing the ganglion. Moreover, synaptic block

was produced by this substance without altering the response of the postganglionic endings to excitation of the ciliary nerve. In other words, the cholinergic synaptic junctions responded to hexamethonium differently than did the cholinergic postganglionic neuroeffector junctions. Extending their experiments to another parasympathetic system, Perry & Talesnik (161) found that ganglionic blocking drugs prevented the cardioinhibitory actions of vagal stimulation, of acetylcholine, and of nicotine. From this they argued that the intracardial synaptic junctions are cholinergic. In conformity with the view that parasympathetic, postganglionic neuroeffector junctions are cholinergic, it was established (162) that denervation of the cat iris results in a fall of the true cholinesterase to 40 per cent of its original level in 21 days.

Addendum

Easton kindly allowed the author of this review to examine an unpublished manuscript (to be published in the *Journal of Neurophysiology*) which has considerable bearing on some of the interpretations of results obtained with internal microelectrodes. According to Easton's interpretation, potentials from end-plate regions of single fibers in frog muscles have, in addition to the potential originating in the membrane of the impaled fiber, a significant contribution from adjacent active fibers. The spikes recorded from the innervation field of a fiber showed various types of distortion according to this external contribution. If Easton's analysis is correct some of the existing interpretations of the compiex records from the junctional region of a muscle will have to be revised or withdrawn. Furshpan and Wiersma (personal communication) also noted in crustacean muscle that intracellular recording from a fiber which did not yield spikes could, nevertheless, show positive potentials as a result of activity in adjacent spike-yielding fibers.

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SOMATIC FUNCTIONS OF THE NERVOUS SYSTEM[1,2]

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"Nothing in all the realm of science comes closer to the things that mean most in human life than the study of the nervous system and how it makes us what we are."[5]

Introduction

Each year new trends in experimental approach and technic are discernible, and over a period of several years there develops a community of modified opinion giving rise to the expression of new and perhaps more comprehensive ways of looking at the nervous system. More information is available concerning time-space patterns in the nervous system especially as they may relate to sensory or motor mechanisms. Responsiveness in a given locus appears related to previous activity or inactivity at that site, and the pertinent time course may be measured in milliseconds, or in days, as with sensitization of denervation. It has become increasingly clear that anatomical and physiological distinctions between visceral and somatic functions, tenable with respect to the periphery, are not so clear within the brain and spinal cord. Not only is there abundant overlap, but there is very little territory which can be said to be "purely" somatic or visceral in function.

Several contributions to general conceptions of neural mechanisms are cited below, but a few with an approach that may be especially helpful to teaching and research follow: Penfield & Jasper (246) reinforce and extend Penfield's conception of the "highest level" or "centrencephalon" lying near the center of the neuraxis. Without unwarranted generalization or oversimplification, these authors assemble the richest stores of experimental evidence on man and animals anywhere available from one institution and try to pin down mental processes and locate them within parts of the brain. The scintillating essays of Walshe (306, 307) and the communications on the parietal lobe by his colleague Critchley (84, 86) constitute some of the most penetrating recent neurological approaches to mind-body problems. A recent communication by Livingston, Haugen & Brookhart deals with the over-all or-

[1] This survey is based upon publications available to us during the period June, 1953 through June, 1954. We make no claim to have covered the entire subject or pertinent literature and beg indulgence for omitting so much.

[2] The following abbreviation has been used in this chapter: EEG (electroencephalographic, electroencephalogram.

[3] John Simon Guggenheim Fellow, 1954–55.

[4] The authors wish to acknowledge the generous time and assistance of Dr. Harald Scherrer, Barbara Harland, and Carle Blasius in the preparation of this manuscript.

[5] Alexander Forbes, President of the Third International Congress of Electroencephalography and Clinical Neurophysiology, welcoming guests to Cambridge, Mass., August, 1953.

ganization of the neuraxis (210). The authors conceive of two vertical sensory and motor systems bound together all along the neuraxis by "transactional mechanisms" which include the association cortex, limbic lobe, and perhaps other parts of the brain, as well as the reticular formation and internuncial pools all along the neuraxis. This transactional component, like the "neuropil" of Coghill, is considered to give the nervous system a dynamic modifiability or plasticity which makes it capable of learning and other complex functions. They suggest that their conception of the vertical organization of the neuraxis is complementary to the Jacksonian ideas of different "levels" and "centres." Following Brookhart's example (56), we are considering the somatic functions of the nervous system in terms of its vertical organization.

Studies on the Input Side of the System

Receptors and conductors.—A symposium on the physiology and pharmacology of receptors and nerve endings held in Stockholm in December, 1952 has been published (286) with contributions from Adrian, Zotterman, and Bullock, to mention only three. Ligaments in the knee joint not connected to muscle nevertheless have nerve endings which supply proprioceptive information (16), and the patterns of discharge along joint afferents correspond closely to the position and motion of the joint (45). Tasaki, Hagiwara & Watanabe recorded action potentials in Mauthner's cells, finding that a single dendritic response lasts so long that the soma can respond repeatedly during that interval (291). Single eighth nerve afferents to Mauthner's cells on each side of the body can excite one while inhibiting the other (258). Although the theory of nerve nets and neurosyncytium (30) survives in some quarters, electron microscopy demonstrates thickened pre- and postsynaptic endings which are separated by about 200 Å of unstructured interval (240). The ultrastructure of nuclear membranes, perikarya, dendrites, and axons reveals numerous mitochondria in cell bodies and dendrites, but few, except at the terminals, in axons (153). Motoneurons respond to ventral root section by a great increase in amount of mitochondria contained in the perikarya (154).

Input into the spinal cord.—The Ciba Foundation symposium on the spinal cord brings together in book form a number of excellent contributions pertinent both to spinal input and output mechanisms (287). Rexed has published a useful cytoarchitectural atlas of the spinal cord of the cat (259). Nerve cells numbering about 5 per cent of the total number in the adjacent grey matter are found in the white matter of the spinal cord (97). An early shoulder in the negative cord potential is taken to reflect presynaptic activity in the terminal portions of afferent fibers (22). Brooks *et al.* infer that intermediate sized A fibers are involved in the initiation and transmission of the dorsal root reflex (58, 187). Recurrent fibers in the dorsal roots, if they exist at all, seem to be extremely rare; recurrent impulses are thought to be attributable to intraspinal activity (145), perhaps the reaction to a chemical agent

(116). In a single fiber analysis, Frank finds that a single dorsal root stimulus may be followed by propagated antidromic dorsal root impulses which may have an effect on subsequent orthodromic impulses (115).

Ascending pathways.—Two neighboring dorsal roots may interact, with the result that some of the impulses traveling in the dorsal columns are eliminated (204). Dorsal column conduction decreases in velocity shortly after entry of the fibers from the hind limb and again in the cervical region, in both instances presumably because of branching and narrowing at these levels (165, 166). Intermittance resulting from fatigue may occur in dorsal column conduction. Like Morin (231), Harwood & Cress find an uncrossed pathway between the posterior columns and medial lemniscus which may be non-synaptic (155). Microelectrode analysis of cuneate nucleus activity suggests some units may be fired repetitively by single imput volleys (13).

Pathways to cerebellum and brain stem.—There is agreement that deep and superficial afferent impulses from one side ascend in both ventral columns to be projected onto tne anterior lobe of the cerebellum (232, 233). This area of cerebellar projection overlaps with that of the dorsal spinocerebellar tract conveying impulses from the same body region, but impulses conveyed in the ventral columns arrive about 1.0 to 1.5 msec. later (66), suggesting a temporal mechanism analogous to that in the cerebral somatic receiving area. Topography in the ventral spinocerebellar tract in the monkey is described (322). Grundfest & Carter reveal a dorsal spino-olivary tract which is contiguous with the dorsal spinocerebellar tract but which apparently synapses and decussates high in the cervical region (142). This represents the principal spinal input to the inferior olive. Fibers ascending in both lateral and ventral funiculi make direct connections as terminal fibers or collaterals with pontine nuclei bilaterally (303). Cutaneous afferents link with an ascending anterolateral fiber system in the cord (42), and a study is begun on spinoreticular connections in the cat (176).

An excellent summary of pain mechanisms and pain perception appears in a monograph by Bonica (43). Yoss suggests there is a pattern of localization within the lateral spinothalamic tract for superficial and deep pain stimuli, the latter ascending in the most dorsolateral position as a crossed tract (323). Kennard in a careful study finds that "pain" stimuli are conveyed bilaterally in the cord and are more scattered and diffused than is generally stated (181). Small myelinated fibers from the tooth pulp have conduction and excitability characteristics resembling A gamma-delta fibers of the cat's saphenous nerve (57). Afferent volleys along these fibers evoke activity in the trigeminal descending root, the brain stem, thalamus, and cortex. There is no evidence that tooth pulp stimulation, generally conceded to be painful, gives rise to slowly-conducted activity such as would be expected from C fibers. Long latency responses to laryngeal nerve stimulation are recorded in the dorsal bulbar reticular formation (194) and cerebellum (193).

Galambos provides a stimulating review of auditory mechanisms (122). Tasaki reports that single auditory fibers are not seen to be inhibited by

acoustic stimulation. Fibers arising from the basal turn of the cochlea respond to tones of any audible frequency whereas those from the upper part of the cochlea respond only to low frequency tones (290). Hilali & Whitfield studying activity in the trapezoid body find a characteristic frequency of response area for each unit, but in the trapezoid body the mean discharge rate is lower than in fibers closer to the cochlea, and there is a smaller increase with increased stimulus intensity (161). They suggest that pulse distributions along given fibers play an increasingly important role in successively higher parts of the auditory pathway, again emphasizing time-space patterning. Stotler studied the superior olive, noting that the lateral superior olivary nuclei receive in part from the homolateral cochlea and in part from the contralateral cochlea, whereas the medial nuclei represent both cochlea in a common neuron (281).

Thalamic relays.—The human thalamus has been studied as to development and anatomical organization (92, 93). In deeply anesthetized cats, Rose & Mountcastle find that repetitive discharges of single thalamic units responding to peripheral stimulation are remarkably constant from trial to trial and that alterations in the strength, rate of application, and location of the stimulus generate modified but consistent patterns (260). They point out also that shortening of the latency for the initial spike with increasing stimulus strength may be attributable to the cumulative effect of shortening latencies at each synaptic station and not necessarily to the opening up of a separate more direct anatomical path. The machine-like precision of these findings contrast with those of an equally careful investigation by Cohen & Grundfest who employ a variety of depths of anesthesia and find little evidence for precise somatotopic localization within the ventral posterior nucleus of the thalamus (76). A given locus in the nucleus responds to widely different sources of afferent stimulation, and the initial thalamic responses to stimuli delivered to two inputs show interaction. In the lateral geniculate, repetitive postsynaptic firing occurs, with low-frequency stimulation affecting only large diameter fibers in the optic nerve, as many as ten spikes being elicited following a single input stimulus (39). Using short bursts of high-frequency stimulation (150 to 600/sec.) fatigue of the geniculate response leaves a synaptic potential which can be analyzed for its time-space pattern within that nucleus (40). Monnier reports that stimulation of the ventral posterior medial portion of the thalamus in man elicits pain referred to the contralateral face and mouth (230), whereas stimulation somewhat more caudad, presumably in the spinothalamic tract, gives rise to pain referred to the contralateral side of the body.

Cortical input.—Cortical responses to somatic, visual, and auditory stimulation exhibit different electrical characteristics at different loci (82). At any given point, the number of spikes in a cortical burst tends to vary from one stimulus to the next more than does the timing of the first spike in a given burst. In studying cortical responses to click stimulation, Mickle & Ades observe an advancing wave front of positive potential traveling over the cortex

(224). This may be interrupted by incisions into the cortex and is therefore thought to represent transcortical propagation. A negative potential thought to originate from diffusely-projecting subcortical auditory centers is not affected by such incisions. Lilly's beautiful methods for simultaneous recording at multiple cortical loci reveal in the unanesthetized animal that auditory stimuli give rise to specific complex traveling electrical patterns within and around the auditory projection area (208). Moreover, spontaneous activity consists of potential gradients developing into figures which grow, travel, and die away reflecting complex time-space patterns which are apparently characteristic for central nervous system activity. [See also the report of Walter's toposcopy in man (308).] Hind has mapped the cat's auditory cortex (162). Pribram *et al.* find that the cortical acoustic area in the monkey appears to include a large part of the parietal operculum (253).

Vestibular responses follow a pathway which decussates in the region of the trapezoid body and ascends to the thalamus between the medial geniculate body and the ventral posterior nucleus. Thence third order neurons project to the posterior bank of the anterior suprasylvian gyrus of the cat (225). Another pathway for vestibular projection to the cortex goes up through the paraflocculus of the cerebellum and from that region to the cerebral cortex area as above (273).

Delivering single volleys to the optic radiations, Bishop & Clare have recorded the cortical response and attempted to analyze the sequence of events as they occur in successive strata of the visual receiving area (37). They suggest that discharges of pyramid cells alternate with discharges of cells having short axons, thus accounting for the phenomena of alternating spikes, large and small. Following responses in the direct visual projection area there is a response in neighboring cortex which is delayed by 1 msec. This "association area" is presumed to be activated by discharge of pyramid cells in layer IV and probably also in layer III of the primary receiving area (72). Some of the pyramid cells of the visual cortex, according to Sholl (270), embrace an area referred to as their connective zone, which includes 2000 to 4000 perikarya. This author has made a careful examination of the geometrical cytoarchitecture of the visual and motor cortices in the cat. The implications of his work are vast [See (83)]. Bagshaw & Pribram, in behavioral studies on the monkey, interfere with "primary" gustatory functions by extensive resection of cortex surrounding the frontal operculum and anterior insula (23). They find the anteromedial temporal cortex to be implicated in taste discrimination.

An investigation of cortical representation of deep sensibility has been published by Adey and associates (2, 3). Deep sensibility overlaps tactile and is represented bilaterally, the homolateral representation lying within the area of contralateral representation, and the contralateral latencies being 5 to 10 msec. shorter. They suggest that "perception and localization may occur in terms of the disposition of points of shortest latency within an activated area."

Amassian has examined single unit activity in the somatic receiving cortex (11). Evoked potentials in the waking rabbit's somesthetic cortex are examined (249). Interaction between incoming volleys from thalamic or tactile stimulation and corticocortical transcallosal activation is described (248). Li & Jasper have mapped evoked responses occurring at various depths of the cortex (206). Impulses from cutaneous and muscular afferents, ascending in the ventrolateral columns of the cord, are projected bilaterally to both pre- and postcentral gyri and persist in the precentral gyrus after bilateral removal of the postcentral cortex (123). Cutaneous and muscular nerve impulses may ascend to cortex along the pyramidal tract by way of direct spinocortical fibers or by way of the dorsal column nuclei (55). These paths appear to provide impulses to the brain stem and motor cortex relating to all four extremities but predominately the forelimbs and especially the distal parts of those limbs. The authors suggest that this ascending pyramidal pathway is important for the coordination of skilled movements and may represent the afferent path for plantar and abdominal reflexes and placing and hopping reactions. Responses which apparently travel otherwise to the precentral cortex may persist after resection of the somatic sensory region, bilateral transection of the pyramids, dorsal columns, or lateral spinothalamic tracts (190).

Studies on the Output Side of the System

Corticospinal projections.—Considerable attention has been devoted to the sites of origin and functional characteristics of the pyramidal tract (61, 195, 304). The "supplementary motor cortex" on the medial surface of the hemisphere contributes to the pyramidal tract independently from the precentral motor cortex (34). Stimulation of this region in man results in complex motor acts resembling climbing, the assumption of postures, etc., and there was no discernible boundary with the primary motor cortex (28, 29). Patton & Amassian believe that the earliest pyramidal response to cortical stimulation is attributable to direct excitation of pyramidal neurons, whereas later deflections result from excitations relayed through cortical interneurons (242). Sensitivity of these later deflections to anesthetics (34, 324) and to strychnine (34) add support to this interpretation. Conduction velocities of the fastest pyramidal fibers in the cat are 35 to 40 m/sec. (38) and in the monkey about 70 m/sec. (33). The latter authors report that motoneurons can be activated monosynaptically along the ipisilateral as well as contralateral corticospinal tract. Pyramidal units may be either activated or inactivated by somatic stimulation and their spontaneous activity is usually decreased by excitation of the brain stem reticular formation (63). Motor responses to different parameters of cortical stimulation have been further analyzed (90, 169). The frequency-conditioned changes persist with stimuli applied directly to white matter after removal of the cortex. Meyers and his coworkers find no evidence from studies on cats and 24 human cases for the existence of a cortical suppressor mechanism (221, 222, 223), but Bucy rejects the finality of this position (62).

Sensorimotor relations.—The importance of sensory input on motor activity has been illustrated by Gellhorn & Hyde (130) and Gellhorn, Riggle & Ballin (132), using cortical stimulation as the test activation; by Lassek (200) who compares motor deficits following dorsal rhizotomy with those following dorsal column interruption; by Lassek & Moyer (201) following rhizotomy in developing animals; and by Twitchell (300) who emphasizes the importance of cutaneous afferents in purposive movements. The functional role (191) and central regulation (177) of muscle afferents was reviewed during the symposium on postural mechanisms at the XIX International Physiological Congress.

Extrapyramidal pathways.—In the cat the mesencephalic tegmentum and reticular formation of the pons and bulb have rich projections from the sensorimotor cortex (168), and corticifugal and olfactory projections converge in the amygdaloid complex. Movements evoked from the caudate nucleus by electrical stimulation are abolished by lesions in the brain stem at the junction of di- and mesencephalon near the midline, leaving unimpaired cortically induced movements (157). This extrapyramidal pathway seems to join the corticospinal pathway lower down, since lesions of the medial portion of the cerebral peduncles abolished both cortically and subcortically induced movements. Part, at least, of the extrapyramidal motor pathways may depend upon cortex, since after chronic decortications some subcortical regions formerly effective may no longer yield motor responses (243). Reciprocal corticocaudate connections have been demonstrated by Harman *et al.* (152), and the influence of the caudate nucleus on electrical activation of the cortex has been demonstrated (269, 282). Widespread connections of the claustrum to neo- and allocortex have been traced (255).

From the striate region descending fibers project to the lateral geniculate, lateral posterior nucleus of the thalamus, pretectal region, superior colliculus, zona incerta, and pons (236), presumably to engage in the regulation of sensory input, control of head and eye movements, etc. Hamdi & Whitteridge have worked out the relations between retina and optic tectum in the pigeon and relate these projections to eye movements (147, 148). The superior colliculus in the cat responds in a localized way under pentobarbital, but under choralosane anesthesia responses are widespread and show variations in latency of single unit responses (111). Reticular formation neurons responding are of a "higher order" than the collicular units and may represent the next stage in the visual reflex path. Warwick continues his investigation of the eye motor nuclei (311, 312, 313). Crosby (88) and Crosby, Yoss & Henderson (89) extend their examination of the central mechanisms governing eye movements. Electromyographic analysis confirms that the ocular muscles undergo truly reciprocal activity (41). Van Eyck & Gernandt describe vestibular reflexes in the pigeon (301). Hood & Pfaltz make the interesting observation that adaptation, as measured by decline in the duration of nystagmus following repeated test rotations, does not occur if the animal is lightly anesthetized (167), and also that no adaptation occurs in response to repeated caloric vestibular stimulation.

Vogt finds that sympathin is concentrated predominately in those brain stem regions especially concerned with autonomic function (302), but which overlap with the reticular activating system and extrapyramidal output mechanisms. Certain parts of the brain stem reticular formation and cerebellum (106, 289) known to have somatic functions appear to be related to micturition. Moreover, removal of the cortical leg area will produce a hypertonic bladder associated with alterations in the pattern of micturition (272). Finally, Landau observes that pyramidal stimulation in decerebrate cats will evoke a variety of autonomic responses including vasomotor, sudomotor, pupillary, gastric, and vesicular (196).

The importance of neck afferents in triggering a coordinated "jump" movement in hypothalamic cats has been reported (144). Hemingway *et al.* have been able to suppress shivering by hypothalamic stimulation (158). Experimental tremor has been reproduced by electrical stimulation of the midbrain tegmentum (113) and bulbar reticular formation (310). Ward & Jenkner suggest that tremor produced by chronic lesions of the basal ganglia or midbrain tegmentum may be attributable to sensitization of denervation. Stimulation-induced tremor is reduced by some anticholinergeric drugs (310), and abnormal involuntary movements in patients may be abolished by some barbiturates (32).

Reflex myoclonic reactions observed under chloralosane anesthesia involve participation of supraspinal structures (presumably the brain stem) (10), whereas in jerks evoked by strychnine, spinal mechanisms are sufficient (7). Nevertheless, paleocerebellar and reticular formation stimulation can affect strychnine tetanus of the spinal cord (294). Reticular formation influence on spinal reflexes (184) and the roles of the reticular formation, cerebellum, vestibular nuclei (277, 278), and spinal "border cells" (276) on postural mechanisms have been explored further. Evidence now indicates that brain stem facilitatory and inhibitory influences may affect postural patterns in a reciprocal manner. In fact, antagonistic motoneurones can respond discriminately to stimulation of the vestibular nuclei or the bulbar reticular formation (295a). Embryological (197) and anatomical (198) studies of the cerebellum are continued by Larsell. Cerebellar inhibitory and facilitatory effects (51, 295) as well as direct motor responses induced by electrical stimulation (186), have been reported. The intimate connections of the cerebellum to the brain stem (54, 317) provide further anatomical bases for the functional unity of these two structures (50, 228, 234).

Final common path and spinal reflexes.—By dint of the most extraordinary patience, Chu has been able to isolate and examine anterior horn cells from the human spinal cord (69). He observes dendritic granulations or "thorns," a smooth axon which narrows before it meets the myelin sheath, and nodes of Ranvier. The phrenic motor nucleus is organized vertically and its dendrites course along its length (141). Dolivo & Fleisch have re-examined the "crossed phrenic phenomenon" and find that activity in a few fibers of the phrenic nerve is augmented immediately when conduction is interrupted

in the phrenic distal to their recording (96). Since such immediate response cannot result from chemical regulation, they suggest that either a flow of inhibitory impulses entering from the diaphragm is cut off or possibly that the phrenic motoneurons may undergo immediate increase in excitability as a result of division of their axons. Downman investigates the splanchnic contributions to spinal reflexes with particular reference to abdominal splinting (99).

Reflex activity in young rabbits may be facilitated if brain stem structures are intact, indicating a temporarily favored path or prolonged internuncial activity, either alternative depending upon integrity of midbrain connections (214). Reflex conduction may be depressed for several seconds by prolonged activation of the circuit (174). All of the motoneurons to a given muscle may discharge synchronously at the peak of posttetanic potentiation (159), and the motor pool can be so prepared by conditioning volleys that different grades of spinal reflex activity can be achieved (173). Intracellular recordings have been made with units activated antidromically (53). Current flow in elaborate patterns in and around grey matter and nervous structures play an important role in integration. On this, temporary changes are superimposed by incoming impulses [Matthews (217)]. A number of other important contributions to spinal reflex mechanisms have been made (8, 9, 75, 90, 108, 143, 175, 239, 244, 316). Facilitation and inhibition of gamma efferents correspond to similar alterations in large motoneuron activity in response to cutaneous stimulation (104). The development of reflex patterns in the kitten are described (215) and are related to progressive development of dendritic activity thought to result from repeated orthodromic activation. The mechanism of "direct inhibition" has been studied by Eccles and associates (46, 81, 100, 101). From a variety of evidence the authors postulate that an increased chloride permeability of the membrane is the underlying mechanism of this inhibition.

Output dependence upon input, and reaction to injury.—Plasticity in the monosynaptic reflex arc is demonstrated by long-term experiments conducted by Eccles & McIntyre (102) and McIntyre (211). Thirty to forty days after cessation of input, monosynaptic activity in both flexors and extensors is reduced whereas polysynaptic discharges are somewhat augmented. A brief burst along the afferent path will restore the monosynaptic channel which remains thus enhanced for hours and may influence adjacent segments. The time sequence of sensitization of denervation following dorsal root section has been examined by Teasdall & Stavraky (292). Testing stimuli delivered to the basis pedunculi after sensitization has developed, the cat being acutely decerebrated, reveal a lowered threshold on the deafferented side and the contraction has a shorter delay and longer duration. Semisection of the cord or semidecerebration gives rise to a similarly developing sensitization (138). Spiegel & Szekely report cortical sensitization following thalamic lesions (274). These findings have an obvious relevance to ablation studies but probably have much greater significance than has hitherto been credited

to them relating to the dependence of normal nervous mechanisms upon a continuing normal input. Experimental nystagmus in kittens raised in the dark is "cured" by letting them have a more luminous input (59).

Ischemia will cause repetitive discharges in normal human motor nerves (74) and sensory loss in patients with partial nerve lesions (133). In regenerating, motor nerves seem to be attracted by something more than contact guidance (164). Regenerating human nerves are capable of closing long distance gaps and the distal stumps appear to influence this regeneration (283). Small parts of muscles, but none of the extracts of muscle thus far tested will influence the process of motor nerve regeneration, and some contact with motor end plates may be necessary for these nerves to mature (109).

Transactional Mechanisms

"Transactional mechanisms" in the nervous system are arbitrarily considered to be those which evidently involve much more than input-output inter-action systems (210). Several complex regions of the brain are included from each of which something more elaborate is obtained than might be predicted from analysis of behavior of the constituent parts—regions in which, apparently, transactions take place. For simplicity's sake the transactional compartment of the nervous system is taken to include, at least, the associative mechanisms of the cortex, mechanisms apparently involved in voluntary movement, central processes regulating sensory input, thalamic relations to behavior, basic neurology of the entire limbic system, brain stem reticular formation functions, and the general phenomena of electroencephalography.

A theoretical consideration of the behavior of large domains of neurons as they might be analogized to interacting "cooperative" populations of atoms suggests that some of the complex waves observed to sweep across the cortex during spontaneous or induced activity may be more comprehensible if examined in terms of group behavior than in terms of unit activity [Cragg & Temperley (83)].

Central associative processes.—Behavioral studies in monkeys indicate that no unique integrative function can be assigned the "association areas" but that certain cortical loci seem to be maximally concerned with specific behavioral capacities (68, 251). Delgado & Rosvold, for example, demonstrate interference with delayed response without interference with visual discrimination on stimulation of the ventromedial portion of the frontal lobe (94). Critchley's monograph on the parietal lobes goes a long way toward reducing the voluminous clinical literature to manipulable porportions and draws conservative conclusions from the sifted and substantial residuum (84). Lhermitte analyzes defects in body imagery associated with parietal lobe lesions in man (205). Denny-Brown reports on parietal lobe apraxia (95) and Hoff on dominance problems in relation to parietal lobe perceptive mechanisms (163). Lesions associated with perceptive reduplication of body parts are also associated with reduplication in other respects, e.g., for

time, place, or person (315). It is suggested that agnosia is due to defective ability to compare and contrast sensory relationships of specific categories (257). Just as vocalization may be induced by stimulus of the medial surface of the frontal lobe and may be associated with epileptic discharge from this region, there may be various impairments of language functions relating to defects here (70).

Lele, Sinclair & Weddell caution against using reaction time to touch for the derivation of conduction velocities since there is great variability in normal subjects from day to day, subject to subject, and testing site to testing site (203). Bender and associates continue his important revelations concerning the ability to identify and localize asymmetrical simultaneous tactile stimulation (31, 112). Some of the neurophysiological mechanisms that may be involved in double stimulation are given consideration by Purpura (254). Amassian has analyzed unit interactions in the somesthetic association areas (12). Perceptual space-time problems are considered by Goody & Reinhold (137) and Martin (216), while Critchley analyzes "tactile thought" as it occurs in the blind (85).

Central command mechanisms.—Penfield finds that the precentral gyrus makes its essential contributions to skilled movements even when separated from its surrounding transcortical connections and that electrical alterations associated with ideation or performance of movement may be limited to the immediate sensorimotor cortex involved (245). He concludes that voluntary movement may be initiated from some subcortical station and that the final integrative processes probably take place in the central neuraxis, the "centrencephalon." Continuing his careful investigation of the motor cortex in primates, Liddell analyzes overlapping functional representation (207). An interesting discussion of volitional movement is offered by Critchley, Bates & Liddell (87).

Lassek reinforces previous evidence relating to sensory contributions to motor performance (199), contributions probably occurring not just at the segmental level but throughout the sensorimotor connecting links along the whole neuraxis. This position is emphasized by Cole & Glees with respect to motor defects following small lesions in the sensory cortex (77). Examination of focal motor and sensory fits reveals patterns which shift in a manner reminiscent of the travelling waves of spontaneous or induced cortical activity (262). Sensory inhibitory auras pass to focal paralysis; focal paralysis did not passs to another kind of aura, but was either self-limited or passed to unconsciousness.

Central control of input.—Evidence that the brain exerts a tonic inhibitory influence on afferent input into the nervous system is presented by Hagbarth & Kerr (146). Moreover, stimulation of the bulbar or midbrain reticular formation, the anterior vermis of the cerebellum, the precentral motor cortex, the first and second sensory areas, and the cingulate gyrus will depress input responses relayed in the dorsal columns, ventral columns, and midbrain, or recorded from the surface of the cerebellum or sensory cortex.

Eldred, Granit & Merton extend observations on the central control of activity in the muscle spindle efferent, thereby also regulating sensory input (105). They find that midbrain reticular formation stimulation can bias activity of the muscle spindle afferent in such a way that with slow stretch the afferent is firing at a rate approaching the maximum attainable early in fast stretch in the de-efferented spindle. It would appear that the central nervous system has as precise control over its input as over its output! Rasmussen continues his observations on descending links in the auditory pathway: fibers from the superior olive to the cochlea and thence to the spiral plexus near the spiral organ (of Corti) suggest the possibility of another mechanism for sensory regulation (256). Perhaps blocking of a tonically acting descending pathway by anesthetics is inferred by the experiments of Merlis & Lombroso who show an increased central and myoclonic response to auditory stimulation under barbiturates (219).

Behavioral changes related to thalamic lesions.—In an extended series of behavioral studies on cats, it was been observed that destructive lesions in the dorsomedial nuclei of the thalamus yield increased irritability, voraciousness, reduced motor activity, and diminished ability to solve learning and discrimination problems (266). Conversely, anterior nuclear destruction is followed by docility and increased responsiveness to pleasurable stimulation. When both nuclear groups are destroyed the animals show overlability in reaction to both noxious and pleasurable stimuli. Destruction of the intralaminar region induces somnolence, lethargy, and a reduced reaction to noxious stimulation.

Reference is made to the Ciba symposium on the spinal cord (287), to the symposium of the Third International Congress of Electroencephalography and Clinical Neurophysiology (284), and to the Laurentian Conferences *Brain Mechanisms and Consciousness* (4a) in each of which, particularly the latter, important communications concerned with transactional mechanisms have been published.

The limbic lobe—Understanding of the functional organization and importance of the limbic system has been advanced especially by the communications of Fulton (120, 121) andMacLean (213). Allison provides a general review of the anatomy of this region (6). Daitz pointed out that there are nearly twice as many fibers in the fornix of a man as in his pyramidal tract and that the relative increase of the fornix over the pyramidal tract in going from monkey to man is 5:2 (91). Adrian observes different patterns of activity generated in the olfactory apparatus by different odors (4). No connections of the lateral olfactory tract with the entorhinal area, the hippocampus, or septal region has been identified, and there is only limited degeneration in the amygdaloid complex (1, 19, 47, 48).

Electrical activity of the hippocampus in conscious rabbits is altered during sexual arousal (139). During arousal from hibernation, the first signs of electrical activity in the brain are detected in the hippocampus, anterior commissure, cingulum, mammillary bodies, and cerebral peduncles (67).

Chatfield & Lyman conclude that the limbic system is active in mechanisms controlling heat production during this arousal process.

Stimulation of the hippocampal gyri in unanesthetized animals evokes "attentive" behavior not directed toward external stimuli. With stronger intensity the animals show evidence of fear, anxiety, or fury. Similar behavior patterns are observed during stimulation of the lateral portion of the amygdaloid complex or the cingulum bundle (15, 177 to 180). EEG[2] arousal in cats and humans has been evoked by amygdaloid stimulation (110). Electrical excitability of the human uncus is described (134). Sloan & Kaada (271) report on the effects of anterior limbic stimulation. Seizure discharges following repetitive stimulation of the fimbria is propagated to other structures by way of the hippocampal commissure (140). Seizures have been induced via implanted electrodes in Ammon's formation by Akert & Andy (5) who note that the animal assumes a frozen position although it reacts to sensory stimuli. Movements of the face and jaw analogous to that observed in psychomotor epileptic attacks may be elicited by stimulation of the amygdaloid in monkeys and of the inferior mesial temporal region in man (25). Schneider & Crosby found that facial movements obtained by stimulating the temporal tip may be combined with movements of the limbs, and, as one moves the stimulus site posteriorly, limb responses alone may be encountered (263). Bilateral removal of the amygdaloid nuclei in cats produces exaggerated oral and vocal behavior, relative docility, and hypersexuality (265) which is abolished by castration and restored by testosterone injections (264). Pribram & Bagshaw relate visual discrimination to the inferior temporal region, locomotor activity to the frontal lobe, taste to the insular region, and suggest that the temporal pole and amygdala are related to food intake and temperature regulation (251).

Evoked potentials appearing over the vertex in man may be related to responses in the cingulate gyrus (26, 124). Small lesions confined to the anterior cingulate region in man result in reduction of pathological worrying and introspection, of timidity and self-consciousness, and of morbid anxiety without apparent loss of sympathy and concern (298). Results in other hands are best with individuals who are overaggressive (103, 202) and least effective for those chronically ill (241). In animals there is a shortened duration of frustration and avoidance behavior without impairment of delayed response (252). Patients with lesions in this region may have "akinetic mutism" (14, 27, 237).

Krieg has published a short monograph depicting frontal lobe connections in the monkey (189). Fulton's Franqui Lectures (119) provide an excellent résumé of frontal lobe physiology and its relations to the cerebellum. The long-term results of frontal lobotomy using matched unoperated controls (218) indicate that improvement is roughly ten times greater in the operated group (4 per cent of controls markedly improved; 88 per cent remained the same or became worse; 44 per cent of the operated subjects reached top adjustment levels, and only 8 per cent remained the same, or became worse).

Moreover, nearly half of the operated group showed improvement even after five years. Heath and his associates have reported on stimulation and recording in the septal region in schizophrenic patients (156).

The brain stem.—An atlas of the cytoarchitecture of the human brain stem (238) and a review of the development, structure, function, and pathology of the human diencephalon (192) have been published. Connections of the midline region of the thalamus (319), links between mesencephalon and hypothalamus in the cat (60), projections of the intralaminar nuclei in the rat (250), and the diencephalic organization of the primitive shrew (65) have been reported. Projections from the rostral brain stem and red nucleus into the inferior olivary complex are described by Stotler (280). The role of the area postrema as an emetic trigger zone is further established by elimination of motion sickness after ablation of this locus (309). A bundle of fibers lying between the area postrema and the tractus solitarius (52) might be the pathway for vagal activation during vomiting. Relatively restricted lesions in the rostral brain stem will limit the capacity of the cerebrum to respond to electric shock with sustained seizure activity, whereas extensive destruction of the thalamus and posterior hypothalamus results in no alteration of threshold for sustained seizure activity (117). The influence of diffuse thalamic projections upon cortex is not necessarily by way of association nuclei (150). The term diffuse in relation to this system is criticized since discrete cortical activation can be produced by finer stimulation technics. Moreover, a topographical organization is disclosed showing that the ventromedian portion of this system is related to the anterior part of the cortex and the dorsolateral portion to the posterior cortical areas, most of the ascending projections apparently passsing through the most anterior portion of the thalamus (149, 151, 171, 172).

Arousal-sleep mechanisms.—Many clinical and experimental observations relating to wakefulness and sleep reinforce the concept of a reticular activating system as described by Moruzzi & Magoun (235). Brief résumés of recent findings are given by Bremer & Terzuolo (49) and Terzuolo (293) (See also 4a). Wolman reports cases of unconsciousness associated with ischemic lesions in the brain stem associated with raised supratentorial pressure (321). Lesions in the hypothalamus are associated with somnolence (275) or coma vigil (314), as well as vegetative disturbances. In experimental animals the degree of somnolence correlates positively with the degree of damage to a tract running from the hypothalamus to the midbrain tegmentum (78). Gellhorn and his colleagues continue to relate arousal functions of the brain stem solely to a restricted part of the dorsal hypothalamus (126–129, 131, 185).

In contrast with the activation obtained by stimulating most afferents, Bonvallet, Dell & Hiegel find that impulses from the carotid sinus baroceptors reduce cortical activity and produce slow waves (44), but whether the effect represents direct inhibition of activating system, direct activation of a hypnogenic zone such as Hess describes (160), or some indirect influence is not established. These same authors report that epinephrine produces cortical

activation which is prevented by intercollicular section. In the cateleptic state induced by bulbocapnine, reactivity of the midbrain reticular substance, cortex, cerebellum, and hypothalamus to afferent stimulation is preserved or even enhanced (288). Following concussion the electrical activity of the cortex is reduced in amplitude and the brain stem reticular formation shows a consistent depression (114).

A systematic exploration of corticifugal pathways to the rostral brain stem reticular formation in the monkey (209) reveals that the frontal eye fields, sensorimotor cortex, paraoccipital region, first temporal gyrus, temporal tip, orbital surface, and medial surface of the hemisphere all project to brain stem regions which have already been demonstrated to function in arousal. It is suggested that these projections might be involved in processes of self-arousal, maintained wakefulness, and focussing of attention (118). Stimulation of these same areas will cause EEG arousal according to Segundo, Naquet & Buser (267). Perhaps such corticifugal pathways are involved in the selective arousal reaction to significant stimuli (18).

Microelectrode studies of the cerebral cortex demonstrate that during arousal the activity of individual units may either increase or be abolished (206, 318). Pyramidal cells are activated during recruiting waves induced by thalamic stimulation (17). A light flash or lateral geniculate stimulation will facilitate motor cortex, but the enhanced excitability does not depend upon the visual cortex or the superior colliculus (305). A pretectal lesion will abolish it, suggesting that perhaps a diffuse arousal mechanism is involved. That visual cortex may contribute to the distribution of visual responses in the brain stem is indicated by the experiments of Ingvar & Hunter (170) who find prolonged latency for such responses after chronic ablation of the visual receiving area. The existence of a diffuse projection system to the cerebellum is inferred from experiments of Coombs (80) who describes the difference between cerebellar responses when there is no central anesthesia (generalized responses) and when anesthesia is employed (localized responses).

Brain waves cannot be explained by simple summation of neuronal spikes or synaptic potentials. Slower processes of excitation with D.C. potential fields, presynaptic and local potentials, electrotonic spread and/or decremental conduction on the neuropil and dendritic plexuses in connection with interneuronal activity must be assumed.[6]

The EEG.—A series of symposia held during the Third International Congress of Electroencephalography and Clinical Neurophysiology, Cambridge, Mass., August, 1953, has been published (284). Topics deliberated during the symposia include: (*a*) recent developments in technique, (*b*) physiological basis of the EEG, (*c*) evaluation of activation of the EEG, (*d*) interrelationships between cortex and subcortical structures, (*e*) the EEG in

[6] Jung, R., during the symposium on the Physiological Basis of the Electroencephalogram (284).

infancy and childhood, and (*f*) characteristics and significance of seizure discharges. A symposium on intracerebral electrography has also appeared (285).

An important review of experimental epilepsy as produced by Kopeloff's technique of injection of alumina cream has appeared (188). Multiple alumina cream injections into the parietal region will yield seizures (71). The effects of acetylcholine and adenosinetriphosphate on electrical activity and their interrelationships are described by Torda (296, 297); of the epinephrine and norepinephrine (227); and of intravenous atropine on normal and epileptic subjects (226). Hearing threshold is identifiable by the EEG (247). Convulsive activity in the cerebellum is followed by silence probably due to exhaustion (229). Cortical and subcortical seizure activity has been examined (279, 320). Slow potential shifts in the cerebrum (98) and the EEG (79) are modifiable by cerebellar stimulation. The effect of drugs on evoked visual area responses and transcortical potentials is reported by Goldring & O'Leary (135, 136).

Circulation and metabolism.—Kety presents an excellent review on cerebral circulation in man (182) and with Landau & Freygang describes a new method for measuring regional circulation in the brains of experimental animals by defining the extent of uptake of an inert radioactive gas (183). Stellate block or ganglionectomy is not likely to be efficacious in relieving cerebral vascular disorders unless the cerebral circulation is slow or the cerebral resistance is high (268). Warming the limbs induces dilation of the pial vessels while immersion in cold water has an opposite effect (107). A detailed study of the vascularity of the motor cortex of the dog is published by Billenstein (35). Tschirgi & Taylor find a steady potential exists between the blood and cerebrospinal fluid (299). During embryonic and foetal development the blood brain barrier becomes less permeable (24). The choroid plexus has been successfully grown in tissue culture and can be made to perform secretory activity in this situation (64). X-irradiation of the head in monkeys results in slowing of EEG patterns, spiking and seizure activity (261), and the blood brain barrier becomes more permeable to trypan blue in certain regions (73). These same regions show astrocytic degenerations not found elsewhere. Approximately similar results are described in response to conventional and high energy radiations (betatron) (20, 21).

Recent monographs.—Several important contributions relating to somatic nervous functions have been published in book form during the year (30, 36, 43, 84, 119, 125, 156, 171, 189, 192, 212, 220, 238, 246, 287).

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VISCERAL FUNCTIONS OF THE NERVOUS SYSTEM[1,2]

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The hypothalamus and pituitary.—The work of Verney (80) on the liberation of the antidiuretic hormone led him to postulate the existence of receptors in the brain capable of detecting changes in tonicity in the blood. These he called osmoreceptors, and he found them in the supraoptic nuclei of four dogs. They have now been studied extensively by Jewell (55), who describes them as vesiculated neurones. The vesicles have a diameter of from 10 to 200 μ and show at one side a cell body of which they are a part. An axon process leaves the cell body, and these processes are heavily loaded with the same neurosecretory material as that described by Bargmann (10), who showed that the fibers of the supraoptic nucleus conducted such material towards the posterior lobe. Palay & Wissig (71) have shown that the neurosecretory granules can be demonstrated in fresh supraoptic neurones by phase contrast microscopy, so that they cannot result from precipitation during fixation. Thus the osmoreceptors are intracellular expansions formed in the large neurones of the supraoptic and paraventricular nuclei. Jewell conceives these vesicles as being changed in size by the tonicity of the blood, the alteration then acting on some form of stretch receptor, thus setting up or modifying impulses in the nerve fiber. The number of vesicles was found to be greatly diminished in animals in which the supraopticohypophysial tracts were divided and which also developed polyuria. It is interesting to note that the possibility that nerve fibers might act as pipe-lines for delivering neurosecretory material was first suggested by Gaskell (41). It is a function not yet discussed by electrophysiologists.

C. von Euler (36) has recorded effects which he calls slow hypothalamic osmopotentials by placing one electrode in the supraoptic region of the hypothalamus and a second in Ringer-agar in the frontal air sinus. He has then injected a certain volume of 2 per cent sodium chloride into the common carotid artery and observed a potential change of about 1 mv. lasting for from 45 to 50 sec. He observed a similar effect when he used 10 per cent glucose, while the same volume of water caused a change in the opposite direction.

Hypothalamic and posterior lobe extracts.—Vogt (82) compared the activity of extracts prepared from the dog's hypothalamus with commercial posterior lobe extract. She found that the hypothalamic extract contained very much more pressor (or antidiuretic) than oxytocic activity, the mean ratio being about 15 to 1. She then compared dog's posterior lobe extract

[1] The survey of literature pertaining to this review was completed in June, 1954.

[2] The following abbreviations have been used in this chapter: TEPP (tetraethylpyrophosphate); DFP (di-isopropylfluorophosphate); ADP (adenosinediphosphate); AMP (adenosinemonophosphate); LSD (lysergic acid diethylamide).

with the same commercial extract and found that in the posterior lobe the amount of pressor activity was the same as the amount of oxytocic activity. Vogt suggests two possibilities to explain the difference between the hypothalamic extracts and the posterior lobe extracts, one, based on the theory of Bargmann (9) and of Bargmann & Scharrer (11), that the posterior lobe hormone is synthesized in the supraoptic and paraventricular nuclei and travels down the supraoptic and hypophyseal tract into the posterior lobe where it is stored. On this theory it would appear that the hormone as synthesized in the ganglion cells undergoes some modification in the posterior lobe which enhances its relative oxytocic activity. The second possibility is that the extracts of the hypothalamus contain vasopressin only, and do not contain any oxytocin at all. Du Vigneaud (81) and Popenoe have prepared a highly purified vasopressin which did not contain any oxytocin as shown by the complete absence of leucine and isoleucine. This vasopressin contained oxytocic activity which was about 5 per cent of the vasopressor potency. Hence it seems that pure vasopressin has some intrinsic oxytocic activity.

Waitzman & Steggerda (84) have observed that extracts of the hypothalamus of the ox have an antidiuretic action, and Lloyd and his colleagues (65) have found that antidiuretic activity disappears from the blood of rats after hypophysectomy, but that it returns to the blood about four weeks later. They think this is attributable to a discharge of the hormone from the hypothalamus.

Paraventricular nucleus and oxytocin.—Olivecrona (70) has described experiments to investigate the relation of the paraventricular nucleus to the pituitary body. He destroyed the paraventricular nuclei without destroying adjacent nuclear areas by using electrolytic lesions in the diencephalon of rats. He found that the thyrotrophic and adrenocorticotrophic functions of the pituitary were unaffected, but that the lesions caused a disappearance of oxytocin from the posterior lobe. When the bilateral destruction of the nuclei was complete, the disappearance was complete, though the content of vasopressin was unchanged. Posterior lobes from animals with lesions near the paraventricular nuclei, but leaving them intact, contained a normal amount of oxytocin. Thus, Olivecrona concludes that the paraventricular nucleus is a hypothalamic center regulating the production of oxytocin by the posterior lobe.

Release of hormones from the pituitary.—The question whether the antidiuretic hormone of the posterior lobe is released alone in response to a specific stimulus, such as a change in blood tonicity, or whether it is accompanied by oxytocin has been studied by Abrahams & Pickford (1) in bitches in which one carotid artery was exteriorized and in which the upper end of one uterine horn was brought out to the flank. Activity in the uterus could then be recorded by inserting in it a balloon which was filled with saline. The ovaries were removed. They found that emotional stimuli, and also intracarotid or intravenous injections of concentrated sodium chloride solution, caused not only an inhibition of water diuresis but also a simultaneous increase in uter-

ine activity which persisted as long as the antidiuretic action. In one animal the supraopticohypophysial tracts were divided after normal activity was observed in the uterus. The day after the operation the uterine activity was greatly reduced, and during the remaining days of the preliminary polyuria it showed scarcely any spontaneous contractions. During the normal interphase the uterus contracted normally, but with the onset of the permanent polyuria it again became quiescent. These results establish that a stimulus which might be expected to be specific for the release of the antidiuretic hormone also releases the oxytocic hormone.

The pituitary and renal circulation.—Evidence that the pituitary body adds a substance to the blood which controls the vascular tone of the kidney has been supplied by Brull & Louis-Bar (17). In previous experiments they transplanted the kidneys to another part of the body and arranged that the arterial supply came from a pump so that the pressure could be varied at will. This pump used the animal's own blood, and the renal veins returned the blood to the animal. They found that over a wide range an increase in the pressure of the blood going to the kidneys did not increase the flow through the kidneys and that the kidney could protect itself against excessive blood flow due to a high blood pressure. They have now repeated these experiments after removing the hypophysis, and 2 hr. later they find that the renal blood flow is obedient to changes in the arterial pressure. In consequence they believe that the pituitary adds a substance to the blood which is responsible for this mechanism which enables the kidney to control its own blood flow. Miles, Ventom & de Wardener (69) have shown that this mechanism is put out of action by cyanide.

Function of pseudocholinesterase.—(This term will be employed because it is the original term, and because later suggestions have not been more satisfactory.) Attempts to link the hypersensitivity of denervated structures to a fall in the amount of enzyme present may claim to have had a limited success (23) but have led to some interesting discoveries. It was found (22) that the degeneration of the sympathetic fibers to the iris led to a fall in the amount of pseudocholinesterase present. This, it was suggested, might be responsible for the increased sensitivity of the iris to epinephrine (adrenaline). A similar finding in the blood vessels of the rabbit ear is described by Grant & Thompson (5, 78) and their colleagues. After degeneration of the sympathetic fibers, either alone or together with the sensory fibers, there was no change in the amount of amine oxidase present, but a large fall in pseudocholinesterase. They also found that extracts of the normal arteries contained acetylcholine, and amassed much evidence to support the view that the constrictor action of epinephrine injected into the arterial lumen is restricted by the fact that it has to overcome the dilator action of acetylcholine which is being continuously formed in the vessel walls. After degeneration of the sympathetic nerves, the acetylcholine and pseudocholinesterase are much diminished, and therefore the constrictor action of epinephrine is, as they find, enormously increased. It should be remembered that both ephedrine

and cocaine which augment the action of epinephrine are inhibitors of pseudocholinesterase as well as of amine oxidase.

Griffin and his colleagues (45) have observed the effect of epinephrine and of norepinephrine in causing changes in resistance to blood flow through the vessels of the dog's leg, making separate observations on muscle vessels and skin vessels. When they compared the action on normal muscle vessels with that on muscle vessels denervated some time previously, they found that the effect of epinephrine was about the same in both. In skin vessels, on the other hand, epinephrine was much more active in vessels previously denervated than it was on normal vessels. Since these results on skin vessels of the dog agree with those of Armin, Grant, Thompson & Tickner (5), it may be that skin vessels are hypersensitive to epinephrine after denervation, whereas muscle vessels are not.

As already mentioned, Grant and his colleagues (5) found no change in the amine oxidase content of rabbit ear vessels after denervation. Smith & Alperi (76) have examined the effect of amine oxidase inhibitors on the reaction of isolated carotid arteries of swine and of dogs. They find that ephedrine and diphenhydramine (Benadryl), both of which inhibit amine oxidase, both potentiate the action of epinephrine on carotid arteries of swine, but not on those of dog. They believe that amine oxidase may play a much more important part in swine than in the dog. Certainly it would appear from the work of Schayer & Smiley (74) that, in the rat, amine oxidase is an active agent in the destruction of epinephrine. They gave epinephrine labelled on the carbon of the N-methyl group to rats and found that ordinarily about half was inactivated by loss of methylamine, presumably through the action of amine oxidase. However, when Marsilid (the isopropyl derivative of isonicotinyl hydrazide) was given, practically all the C^{14} was excreted in the urine, indicating that Marsilid, which is an inhibitor of amine oxidase, prevented the loss of C^{14} as methylamine.

Cholinesterase in glial tumours.—Bülbring, Philpot & Bosanquet (21) found that cholinesterase activity was present in glial tumours in larger amount than in normal cerebrum, and in similar amount to that in the thalamus, midbrain, and cerebellum; moreover, the activity was mostly attributable to pseudocholinesterase. They also found amine oxidase and norepinephrine to be present. They consider that neuroglia participates in the formation and breakdown of substances which act as humoral transmitters besides serving as a supporting and nutritional tissue. Augustinsson & Heimburger (8) have described a method for the determination of cholinesterases of blood absorbed in small amounts on filter papers.

Sympathin in the brain.—The distribution of epinephrine and norepinephrine (the mixture being called sympathin) in the brain has been studied by Vogt (83). She found the highest concentrations in regions which contain the diencephalic, mesencephalic, and bulbar representations of sympathetic activities; also in the area postrema at the hinder end of the fourth ventricle

(though this is not nervous tissue proper, perhaps having a chemoreceptor function (14, 24a, 85) in relation to the dorsal nucleus of the vagus).

Some substances such as morphine, apomorphine, and β-tetra-hydronaphthylamine when acting for 3 hr. caused a fall in the concentration of the hypothalamic sympathin. The substances which had this effect also depleted the adrenal medulla by their central action (i.e., not if the splanchnics were cut). Other substances such as caffeine caused no fall either in the concentration of hypothalamic sympathin or in that of sympathin in the adrenal medulla. The effects of different substances on the sympathin in the two places were parallel.

Strong reasons are given for supposing that the sympathin in the brain is not merely that present in the vasomotor nerves. It is pointed out that practically all effects mediated by the sympathetic nerves can be elicited from the hypothalamus, which is rich in sympathin. Moreover, higher centers such as the anterior and medial thalamic nuclei which are believed to be relays for the transmission of hypothalamic stimuli to cortical areas, are also very rich in sympathin, being for example four times as rich as lateral thalamic nuclei which have no hypothalamic connexions. The function of this sympathin awaits further investigation.

Lindgren & Uvnäs (64) have studied vasodilator responses produced in the muscles of the hind leg of the dog by stimuli applied to points of the medulla oblongata and reaching the muscles by way of the sympathetic outflow. They found two areas from which vasodilator responses could be elicited, one close to the midline in the central part of the rhomboid fossa, and the other, not previously described, in a more lateral position. The responses from this second area were abolished by atropine, and therefore transmitted by cholinergic fibers in the sympathetic supply.

Peripheral ganglia in blood vessels.—Evidence that nicotine causes the liberation of an epinephrine-like substance either from ganglia or from chromaffin tissue has been obtained for the intestine by Ambache (2, 3) and in the cardiac atria by Kottegoda (60). The action of nicotine and of acetylcholine in the perfused rabbit ear has now been studied (61), and some longstanding puzzles have been explained. In 1914 Dale (27) found that acetylcholine caused dilatation of the ear vessels while Hunt (54) the following year denied this, saying that acetylcholine caused constriction. Kottegoda has shown that both are true and that, in the presence of atropine, acetylcholine causes constriction. Since nicotine also causes constriction, he determined the effect of both these substances in the presence of hexamethonium, and found that the constriction they caused was abolished. The constriction appeared to be a result of the liberation of an epinephrine-like substance, since in the presence of an agent which reversed the action of epinephrine, the constrictor action of nicotine and of acetylcholine was converted to a dilator action. He also showed that in the ear perfused for many hours, in which the action of acetylcholine is usually constrictor even in the absence

of atropine, the removal of the skin left a network of vessels over the surface of the cartilage through which perfusion could be continued. Since the action of acetylcholine on these was purely dilator, it appeared that the constrictor reaction was attributable to the presence of a nervous mechanism in the skin. Ginzel & Kottegoda (43) have shown that the constrictor reaction persists after degeneration of the sympathetic fibers and also after degeneration of both the sympathetic and sensory fibers. This suggests that the constrictor effect is exerted by the action of nicotine and acetylcholine on some ganglia or nerve fibers or chromaffin tissue which escapes degeneration after sympathetic and sensory fibers are removed.

Hilton (49) has obtained somewhat similar results in the gastrocnemius muscle of the cat. When nicotine is injected into the artery it causes dilatation followed by constriction. The constriction is abolished by phentolamine (Regitine); it is not affected immediately by section of the sciatic nerve but disappears when the nerve has degenerated. The constrictor response is also absent after removal of the lumbar sympathetic chain and ganglia, and Hilton therefore concludes that nicotine elicits axon reflexes in sympathetic nerve fibers in skeletal muscle, and considers this conclusion to be in line with the previous observations of Coon & Rothman (26) of similar axon reflexes in mammalian skin. The evidence of Coon & Rothman was that the injection of acetylcholine and nicotine into the skin of the cat's tail caused erection of the hairs, and they stated that this effect was absent when the sympathetic fibers had degenerated. However, they gave no details of the experiments in which the sympathetic ganglia were removed, nor did they state how many they performed. Since their paper was otherwise fully documented, and since the removal of all lumbar sympathetic ganglia is difficult, caution is necessary in accepting this particular conclusion, and similarly caution is necessary in accepting Hilton's conclusion about the effect of lumbar sympathectomy in his experiments. Here, also, no details were given of the experiments or of their number, and no illustration was provided. The idea that nicotine can stimulate a motor sympathetic nerve ending and cause an axon reflex implies that a motor nerve ending is structurally similar to a sensory nerve ending, which is most improbable. A sensory nerve ending is an organ for receiving stimuli, and there is nothing strange in supposing that nicotine can activate it. A motor nerve ending, so far as we know, has no receptors on which nicotine can act; the idea of substances "acting" on motor nerve endings was dropped many years ago. Hence, Hilton's conclusion that nicotine "far from acting in a specific manner at autonomic ganglia . . . is quite indiscriminate in its effects on nervous structures" seems premature and requires far stronger evidence than has yet been given.

Carotid body and carotid sinus.—There was much discussion of the action of acetylcholine and nicotine on the carotid body at the Philadelphia Symposium (28, 30, 63); here the situation is similar to that of the sensory receptors in the skin of the cat which were examined by Douglas & Gray (31). In both places acetylcholine and nicotine will stimulate, but, when their action

is blocked by hexamethonium, the normal physiological stimulus, oxygen want in the body and mechanical pressure on the skin will still excite. Heymans and his colleagues (47) describe experiments which do not support the view that acetylcholine plays a role as chemical transmitter of excitation in the carotid sinus baroreceptors or in the chemoreceptors of the carotid body. On the other hand, Diamond (29) used an isolated carotid sinus preparation, recording from the sinus nerve, and perfused it with oxygenated Krebs-Henseleit solution at 37°C. The pressor-receptors responded to various constant pressures, just as they did in blood-perfused sinuses (62), for as long as 7 hr. Injections of 0.5-1.0 μg. acetylcholine or of nicotine into the perfusing fluid caused increased firing from active pressor-receptors and a discharge from some whose threshold was above the perfusion pressure used. The effects of acetylcholine persisted in the presence of atropine, and were therefore not attributable to an effect on smooth muscle, but were abolished by hexamethonium. The hexamethonium had no effect on the discharge produced by the pressure.

The evidence makes it likely that the situation is similar for stimulation (*a*) of sensory fibres in the skin, (*b*) of baroreceptors in the carotid sinus, and (*c*) of chemoreceptors in the carotid body. Acetylcholine probably increases the rate of firing from receptors already active and brings into action those not firing because the stimulation they were receiving was subthreshold. In excess, acetylcholine diminishes the activity. Acetylcholine is thus modifying the firing from the receptors, but not initiating it. The controversy at the Philadelphia Symposium arose because of the view expressed by Liljestrand that acetylcholine acted as a transmitter. It is evident that acetylcholine has a function at the receptors in the carotid body, but it seems not to act as a humoral transmitter. There is increasing evidence that it has other functions, and acts in other ways.

Action of acetylcholine on sodium transport.—Kirschner (56) has studied the transport of sodium ions through the skin of the frog. They appear to move from inside to outside and also from outside to inside, but in the conditions of his observations, made on an isolated piece of skin, there was a net inflow. When tetraethylpyrophosphate (TEPP) was in contact with the inside of the skin, there was an initial increase in inflow followed by a decline to a point at which inflow and outflow were the same. Physostigmine had the same action. TEPP[2] and physostigmine had little effect when placed on the outside of the skin. When the outside of the skin was exposed to atropine, however, there was a large increase in the inward transport of sodium.

Another example of a function of acetylcholine in relation to ion transport has been described by Koch (57). The fresh water crab *Eriocheir sinensis* has a renal mechanism which is very imperfect for retaining sodium. It, therefore, is obliged to absorb sodium through its gills, and the absorption of sodium by an isolated gill can be studied. Shaped like a miniature ostrich feather it can be floated in a well aerated solution of sodium chloride, and the conductivity of the solution can be measured electrically. As the sodium is

absorbed the conductivity falls, and a record of the fall in relation to time can be obtained. Koch, Evans & Schicks (58) studied the effect of adding dyes to the fluid from which sodium was being adsorbed. They found that whereas acid dyes had no effect, basic dyes like methylene blue inhibited the absorption of sodium, the effect being reversible. Since some basic dyes have an anticholinesterase action Koch tested physostigmine, DFP[2] and TEPP[2] and found that they also diminished the sodium absorption and that TEPP blocked it irreversibly. The cholinesterase of the gills is on the outside, and the action of the inhibitors is exerted only when they are placed outside. My colleague Dr. Vaughan Williams remarked that the acetylcholine might be produced on the inside, and then a sodium ion on the outside might exchange with an acetylcholine ion on the inside. The acetylcholine ion would be destroyed when it arrived on the outside, and its destruction would be necessary for further sodium transport. Koch points out that the active transport of sodium by the anal papillae of the larvae of *Chironomus plumosus* is effected in the same way.

Acetylcholine as a local hormone.—The hypothesis that acetylcholine can act as a local hormone has received support from observations of ciliary movement in the gill plates of the mussel *Mytilus edulis* (20). The movement has been studied in the gill plates by excising them and observing the rate of transport of graphite particles. It has also been studied by the use of a stroboscope which enabled the rate of the ciliary beat to be determined directly in an isolated gill filament. By both methods it was found that low concentrations of acetylcholine and also low concentrations of physostigmine increased the ciliary activity, while higher concentrations decreased it. All concentrations of *d*-tubocurarine decreased the ciliary activity. The presence of acetylcholine in the gill plates was established both by pharmacological analysis and by separating it on a chromatograph. The presence of true cholinesterase and of choline acetylase was also established. Since the gill plates do not contain any nerve fibers it appears that the ciliary beat is controlled by the local formation of acetylcholine, and that this is not acting as the transmitter of nerve impulses.

Transmission of sensory impulses.—Hitherto, nothing has been known of how sensory impulses arriving in the spinal cord are transmitted. When sensory fibers are stimulated it is known that impulses pass in an antidromic direction and that, arriving at the periphery, they produce vasodilatation. It is possible that the substance responsible for the vasodilatation is also the substance which is released at the end of the sensory fiber in the spinal cord and that it is the transmitter. Recently Holton & Holton (50, 51, 52) have suggested that this substance may be adenosinetriphosphate (ATP) and their evidence is strong. They have studied antidromic vasodilatation in the rabbit ear and since it is not affected by atropine or by an antihistamine they conclude that the substance producing it is not acetylcholine or histamine.

Celander & Folkow (24) agree with the findings of Holton & Perry (53) that the substance responsible for vasodilatation on antidromic simulation

of sensory fibers is not histamine or acetylcholine, since the effect of antidromic stimulation is to produce a much too prolonged effect, and since it is not affected by atropine or by pyrilamine (mepyramine). However, antidromic vasodilation is greatly reduced by an anticholinesterase. This strange observation is also true of the dilatation produced when extracts of dorsal roots are injected, and this indicates that the substance released when sensory fibers are stimulated is present in dorsal roots. Since the vasodilator action of ATP is also reduced or abolished by an anticholinesterase, the Holtons have analysed extracts from dorsal and ventral roots of horses by different methods. They have tested their vasodilator action on the rabbit ear vessels; they have measured specific light absorption at 260 mμ., and they have determined labile phosphate by enzyme methods. The results show sufficiently close agreement to justify the conclusion that all the vasodilator activity of these preparations is attributable to a mixture of ATP and ADP[2] with small amounts of further breakdown products. The vasodilator activity of ATP and of spinal root extracts is destroyed by acid and is slightly decreased by alkaline treatment. Since substance P is destroyed by alkaline treatment, it is not the substance chiefly responsible for antidromic vasodilatation, though it may play a small part (46).

One of the most interesting features of this work to the writer is the effect of substances like physostigmine and neostigmine in abolishing the vasodilator action of ATP and of antidromic stimulation. Attention has already been drawn to the work of Grant, Thompson and their colleagues (5) which showed the presence of acetylcholine and pseudocholinesterase in the arteries of the rabbit ear and their disappearance, partial after sympathectomy and complete after sensory denervation. The following argument suggests itself. Since physostigmine abolishes the vasodilator action of ATP, cholinesterase must play a part in the vasodilator action of ATP. If cholinesterase plays a part, then acetylcholine plays a part. What relation exists between ATP and acetylcholine? The answer to this is that ATP provides the energy for the synthesis of acetylcholine by choline acetylase. How can this synthesis be affected by physostigmine or neostigmine, since their effect is on cholinesterase and not on choline acetylase? Perhaps, by inhibiting cholinesterase, they stop the supply of choline necessary for the synthesis of acetylcholine. Such a conclusion would indicate a cycle of acetylcholine synthesis and breakdown proceeding all the time in the wall of the artery. It would also indicate that the vasodilator action of ATP is not a direct action of this substance, but an indirect action resulting from a sudden increase in the amount of acetylcholine formed within the wall of the artery. Moreover, if ATP is the transmitter at the central end of the sensory fibre, it may act there in the same way.

Not only ATP, but also ADP and AMP[2] have a vasodilator action. The action of the latter is mainly on the arteries, while that of the two first is also exerted on the capillaries.

Denervated salivary glands.—Emmelin (32) has continued his work on the

salivary glands, and has extended his observations on the "paralytic secretion" of saliva which follows degeneration of the fibers of the chorda tympani. Having previously shown that the cells of the submaxillary gland become hypersensitive to chemical agents, he has now examined the ganglion cells, to which the chorda fibers are preganglionic. His work has been carried out in cats in which he divided the lingual nerve on one side from two to four weeks previously. In performing his experiment he removed both superior cervical ganglia and the adrenal glands, cut the other lingual nerve, and then found that nicotine caused a salivary flow on the operated side in an amount which had no action on the other side. Thus it was evident that the ganglia from which the influence of the preganglionic fibers had been removed were much more sensitive to nicotine. Since the glands of the denervated side were highly sensitive to epinephrine, he excluded the possibility that nicotine might act by liberating epinephrine by giving dihydroergotamine.

Emmelin & Strömblad (35) have observed a small flow of saliva in unanaesthetized dogs after disconnecting the gland from all known nerves, and they believe that this secretion is attributable to impulses from the central nervous system passing to the gland by fibers hitherto undescribed. The secretion is increased by the smell and sight of food.

Saliva from a normal gland causes a fall of arterial pressure when injected intravenously, as little as 0.001 ml. being active. Emmelin & Henriksson (33) find that section of the chorda tympani greatly reduces this depressor action. The reduction runs parallel to the increase in the sensitivity of the gland to epinephrine. Similar changes were produced without section of the chorda by giving an atropine-like substance daily; this also resulted in increased sensitivity to epinephrine and diminished depressor action of the saliva. The authors suggest that the depressor substance is the Kallikrein of Frey, Kraut & Werle (39), and that it is mainly present in the demilune cells. These cells are particularly affected by section of the chorda, which causes them to be greatly reduced. This would agree with the observation that saliva from the sublingual gland has little depressor action, since the sublingual gland contains much less Kallikrein than the submaxillary; moreover, the sublingual gland consists mainly of mucous cells.

Hypersensitivity after denervation in the spinal cord.—Teasdall & Stavraky (77) have continued their examination of the effects of denervation in the spinal cord. They cut the posterior roots on one side from L3 to S3 in a series of cats, and at various intervals afterwards they tested the effect of stimulation of each side of the basis pedunculi, which produced a flexor response of the corresponding hind leg. During the first four days after the operation the response of the operated side was either less than or equal to that of the normal side, but from then onwards the threshold of stimulation was lower on the operated side. The authors conclude that removal of the afferent spinal neurones led to an increase in the excitability of motor neurones to impulses passing along the corticospinal pathway.

5-Hydroxytryptamine.—Much work is being done to discover the function

of hydroxytryptamine. Welsh (87) has found that it has an intense stimulating action on the heart of the mollusc *Venus mercenaria*, producing effects in concentrations as low as 10^{-10} *M*. The stimulant action of epinephrine and norepinephrine is much weaker. Furthermore, ergot alkaloids such as ergotoxine and ergometrine (ergonovine) exert a prolonged stimulant action on the *Venus* heart which is of interest, because lysergic acid (which is present in the ergot alkaloids) contains a similar indole structure to hydroxytryptamine. Welsh suggests that hydroxytryptamine may be the humoral transmitter of the excitatory nerves to the *Venus* heart. He has gained support for this view (88) by finding that nerve ganglia from molluscs contain mixtures of substances which excite and inhibit the *Venus* heart. He was able to block the inhibitory substance by the use of "Mytolon"[3] and the excitatory substance by the use of the diethylamide of lysergic acid, which is a highly specific antagonist of hydroxytryptamine. Further, he has been able to establish that the ganglia of *Venus mercenaria* and of the whelk *Busycon* contain 5-hydroxytryptamine and acetylcholine, using chromatographic and biological tests. Thus evidence that 5-hydroxytryptamine may function as a humoral transmitter is obviously of the greatest interest.

Observations have been made in mammalian tissues by Gaddum & Hameed (40) on the site of action of hydroxytryptamine. They consider that this substance stimulates certain receptors which are specific for it, since it continues to act in the presence of atropine, in the presence of mepyramine (which blocks histamine) and in the presence of piperoxan (which blocks epinephrine). With regard to these receptors specific for hydroxytryptamine, they have observed certain differences. The diethylamide of lysergic acid is a very active antagonist on the rat uterus and on the vessels of the rabbit ear, but not on the guinea-pig ileum. On the ileum the effect of hydroxytryptamine is blocked by cocaine, and therefore they think that the stimulant action on the ileum is a result of an action on ganglion cell receptors and not on muscle receptors, as when it acts on the rat uterus. Moreover, hydroxytryptamine in excess blocks its own action on the ileum. Hence they compare the effect of hydroxytryptamine to that of acetylcholine. On muscle receptors the action of the former is abolished by LSD[2] and that of the latter by atropine. On ganglion cell receptors the action of hydroxytryptamine is abolished by excess of itself and not by LSD, just as the action of acetylcholine is blocked by excess of itself and not by atropine. Finally, the site of action of hydroxytryptamine on the ganglion cell is different from that of nicotine since hydroxytryptamine acts in the presence of excess of nicotine and since nicotine acts in the presence of excess of hydroxytryptamine. This conception avoids the interpretation suggested by Rocha e Silva, Valle & Picarelli (73) that hydroxytryptamine acts on the course of postganglionic nerve fibers, which was difficult to accept.

Effect of epinephrine on ganglion cells.—The depression of ganglionic

[3] Reported to be 2,5-bis(3-diethylamino-propylamino) benzoquinone bis(benzylchloride).

transmission by epinephrine was first observed by Marazzi (68) and has been often confirmed. The observation of Bülbring & Burn (19) and especially of Bülbring (18) in the perfused cervical ganglion that small amounts of epinephrine facilitate transmission is now supported by other observations. Malméjac & Chardon (67) have perfused the left solar plexus of a dog with blood from another (adrenalectomized) dog and have stimulated the splanchnic nerve. They recorded the effect of the stimulation by the changes in the kidney volume, the kidney being perfused by the blood of a third dog. The infusion of epinephrine in the amount of 0.5 μg. per kg. per min. into the blood going to the solar plexus increased the effect of splanchnic stimulation and also the effect of injection of acetylcholine in causing vasoconstriction in the kidney. Larger amounts of epinephrine had the opposite effect. Giotti (44) has studied the behaviour of the atria of the guinea-pig heart suspended in a bath and has found that as time goes on the inhibitory action of nicotine steadily declines and disappears. However, the inhibitory action is restored when an amount of epinephrine is added to the bath which has no effect of its own. He considers that epinephrine restores the excitability of the parasympathetic ganglia. Gerard (42) has stated that 1 μg. or less of epinephrine or norepinephrine may facilitate leg movement on stimulation of the motor cortex in the cat, while 10 μg. or more cause a prompt and lasting suppression.

Gastric secretion.—The mechanism by which histamine produces a secretion of hydrochloric acid by the gastric cells is still unknown. Thompson & Vane (79) have made the curious observation that, when the stomach of a cat is perfused with the cat's blood, the venous effluent returning to the cat, the amount of histamine which must be infused is the same whether the infusion is intravenous or whether it is intra-arterial. They expected to find that, by infusion into the coeliac axis so that the blood went immediately to the stomach, a small amount of histamine would suffice to produce a large secretion. The work was continued by Born & Vane (15) who examined the possibility that when histamine was infused intravenously it accumulated in the blood, whereas when infused into the gastric circulation it was largely inactivated by the liver. They found that this was not so, but discovered that when histamine was infused into the perfusion circuit as far away from the stomach as possible, it had a much greater secretory action than when infused close to the stomach. On "distant infusion" intra-arterially, from 3 to 5 μg. histamine per min. was as effective as 15 μg. histamine per min. intravenously. Moreover, an infusion of histamine (from 1.5 to 10 μg. per min.) in the distant position was much more effective than the same infusion near to the stomach. The results suggest that histamine acts indirectly upon the secretory cells of the stomach, and that an interaction between histamine and blood may be necessary before secretion can occur. It is difficult to imagine what sort of change can occur when histamine is mixed with blood which enables the histamine to exert a greater secretory action. However, a clue of this kind may prove valuable. Bowie, Darlow & Murray (16) have investigated the action of fluoride on the secretion of gastric acid

caused by histamine and have found that the secretion of acid was readily abolished, concentrations of sodium fluoride as low as 0.005 *M* being effective. Removal of the sodium fluoride was at once followed by restoration of the secretion to histamine. Secretion of pepsin was not inhibited by fluoride and in one experiment was greatly increased. The mechanism of the action of fluoride is becoming of great interest. Recently Loewi (66) demonstrated that small amounts increased the amplitude of the beats of the isolated frog heart, both normally and also when depressed by high potassium, or by low calcium, or by the hypodynamic state.

Substances causing pain.—Keele and his colleagues (6) have described a method of studying pain produced by chemical substances in which they make a blister with cantharidin on the arm of a human subject and then remove the epidermis. Substances to be tested are then applied to the exposed dermis, and the subject records his pain on a drum by rotating a handle which compresses a rubber bulb. Acetylcholine caused him pain in a concentration of 10^{-5} gm. per ml., and histamine, 10^{-3} gm. per ml., caused immediate pain followed by itching. The fluid taken from a blister caused pain which in its onset and duration resembled that caused by hydroxytryptamine (10^{-5} gm. per ml.). Other inflammatory exudates contain an active substance like that present in blister fluid (4), but this substance differs in its properties from hydroxytryptamine in being much less stable, and in being precipitated by acetone from an active exudate, whereas hydroxytryptamine is extracted by acetone. The pain-producing substance stimulates the rat uterus, but its action is not antagonized by dihydroergotamine, whereas that of hydroxytryptamine is antagonized. There is reason to identify the pain-producing substance with bradykinin.

Histamine liberators.—The action of a substance which is known to be effective in causing a liberation of histamine from the tissues has been studied by Feldberg & Talesnik (37). They injected compound 48/80[4] into the saphenous artery of dogs and found that it produced edema which lasted for several hours, and a depletion of the histamine in the skin which lasted for several weeks. It has been doubted whether various histamine-like effects such as the edema produced by egg-white are really a result of the liberation of histamine. This doubt has now been removed since this form of edema can no longer be produced when the histamine in the skin is first reduced. Similarly, when rats are rendered sensitive to light with haematoporphyrin, exposure to light produces redness and edema of the ears, legs, and face. If the skin histamine is reduced by the injection of a histamine liberator, then the rats treated with haematoporphyrin no longer suffer on exposure to light.

Blood histamine and the adrenals.—There are many reasons for suspecting

[4] Commonly spoken of as 48/80. It is a condensation product of *p*-methoxyphenethyl-methylamine with formaldehyde, probably a mixture of the dimer, primer, and tetramer.

that the cortical hormones may control the amount of histamine in the blood, such as the dramatic effect of cortisone in status asthmaticus. Code, Dews & Higgins (25) have studied the effect of adrenalectomy on blood histamine in rabbits, but have failed to observe that the removal of the glands causes any change. Even the development of acute adrenal insufficiency in rabbits adrenalectomized several weeks previously was not accompanied by any consistent change in blood histamine. When cortisone was given either to normal or to adrenalectomized rabbits there was no change in the blood histamine, though the lymphocytes decreased.

Histamine liberation and lymphagogue action.—Since the time of Heidenhain it has been known that extracts of lobster, crayfish, and mussels have a lymphagogue action, that is, promote lymph formation. The accounts of their action given by Heidenhain and by Starling suggested to Paton (72) that they might act by liberating histamine. He therefore injected decoctions of alcohol-extracted mussel into the perfused skin of the cat and found that they released histamine in large amounts. Paton calculates that a whole lobster might release from 5 to 10 mg. histamine. Alongside these experiments he has tested known histamine liberators to see if they act as lymphagogues, by cannulating the thoracic duct and measuring the rate of flow. He found that propamidine, *d*-tubocurarine, or morphine caused an increase in the rate up to twentyfold. Thus it appears that the lymphagogue action of these substances, and some of the effects of eating too much lobster, result from the liberation of histamine.

Gastrin as a histamine liberator.—Emmelin & Kahlson (34) have previously suggested that gastrin may not act directly on the parietal cells of the gastric mucosa, but indirectly through release of histamine, and Smith (75) has now shown that a preparation of gastrin which was almost free from histamine acted as a histamine-liberator when injected into the fluid perfusing skeletal muscle and skin. He also found that when gastrin was injected into the distal aorta so as to reach the skin and the muscle of the lower extremities first, it was just as active in causing gastric secretion as when injected into the celiac artery. Smith suggests that this means that gastrin acted in both cases by liberating histamine. In support of this he found that when the stomach was perfused with Locke's solution, the intraarterial injection of gastrin caused the appearance of histamine in the venous effluent.

Histaminase inhibitors.—Just as the effects of acetylcholine can be potentiated by inhibitors of cholinesterase, so it would be expected that the effects of histamine could be potentiated by inhibitors of histaminase. Arunlakshana, Mongar & Schild (7) have demonstrated that such effects are obtained in isolated organs, namely, the isolated ileum, the tracheal chain, and the uterus of the guinea-pig. Increasing potentiation was obtained with semicarbazide in concentrations up to 10^{-6}. Higher concentrations caused less potentiation, and still higher ones caused depression. Other antihistaminases having similar effects were hydroxylamine, cadaverine, and B_1-pyrimidine. The authors were able to show that the potentiating activities of the different

compounds were correlated with their activities in inhibiting histaminase, and also they showed that the various tissues in which histamine effects were potentiated did in fact contain histaminase. They also showed that compounds not destroyed by histaminase were not potentiated by histaminase inhibitors. It is interesting to note that the effects of histamine on the cat's arterial pressure were not consistently potentiated. These experiments appear to establish that histaminase normally plays a part in determining the magnitude of histamine effects, just as cholinesterase plays a part in determining the magnitude of acetylcholine effects.

Amine oxidase.—Methods for the histochemical detection of monoamine oxidase have been described by Blaschko & Hellmann (12) and by Koelle & Valk (59). The part played by this enzyme is still uncertain. Blaschko & Philpot (13) suggest that it is a catalyst of importance in the metabolism of hydroxytryptamine as well as of the sympathomimetic amines. They compared the rate of oxidation of hydroxytryptamine and of tryptamine with that of tyramine, using the liver and kidney of guinea-pig, cat, and pig. They found that the relative rate of oxidation of tryptamine and hydroxytryptamine was much less in the cat than in the guinea-pig. In the pig tryptamine was oxidised as fast as tyramine, but hydroxytryptamine much more slowly. These differences may indicate that there are different forms of amine oxidase as of cholinesterase.

The changes in the response of the nictitating membrane to sympathomimetic amines which occur after denervation were attributed by Burn & Robinson (23) to loss of amine oxidase. Fleckenstein & Bass (38) point out that the effect of denervation is exactly like the effect of administering cocaine. They therefore think that the effect of denervation is attributable to the cessation of the liberation of the transmitter, norepinephrine, from the nerve endings.

Welch & Blaschko (86) have described the localization of epinephrine in the adrenal medulla of the ox as being partly in the cytoplasmic cell sap and partly, indeed mostly, in the particulate fraction which is separated by centrifugation in isotonic sucrose at 0°C. They consider that these particles which contain the epinephrine may be mitochondria, but they refrain from assuming this and call them presecretory granules. When the fresh undenatured particles were injected into the spinal cat the arterial pressure rose to a maximum equal to that attained by the injection of one-fifth of their epinephrine content, but the return of the arterial pressure to normal was slower than after an injection of epinephrine. Similar observations have been made by Hillarp, Lagerstedt & Nilson (48).

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HIGHER FUNCTIONS OF THE CENTRAL NERVOUS SYSTEM[1,2]

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This chapter heading has boundaries which are somewhat diffuse and intermingled with other topics. It is unlikely that all of its ramifications can be covered adequately in any one annual review. Therefore, a brief summary of what has been covered heretofore will be sketched, so as to permit the materials now surveyed to be viewed in proper perspective and provide some continuity.

Harlow (18) covered the period from 1949, when the last review of Physiological Psychology appeared, to mid-1952. He selected as his central theme—cortical localization of intellectual functions. During the period 1949–1952 the following important books on higher functions of the nervous system appeared and were discussed by Harlow relative to his central theme: *The Organization of Behavior* by Hebb, 1949; *Selective Partial Ablation of the Frontal Cortex*, edited by Mettler, 1949; *Functional Localization in Relation to Frontal Lobotomy* by Fulton, 1949; *The Cerebral Cortex of Man* by Penfield and Rasmussen, 1950; and *Cerebral Mechanisms in Behavior: The Hixon Symposium*, edited by Jeffress, 1951. The material from these books was integrated with recent experimental findings and discussed by Harlow under three major headings: Frontal Lobe Syndrome; Posterior Association Area Syndrome; and Cortical Localization, Mass Action, and Equipotentiality.

Malmo (45), dealing with the period from mid-1952 to mid-1953 covered a wider range of psychophysiological topics. Beginning with an over-view of Eccles' *The Neurophysiological Basis of Mind*, the concepts of synaptic excitation and inhibition, and the structural modeling of the nervous system, were related to Pavlovian conditioning and other aspects of learning. Psychological problems of reactive inhibition, drive, and motivation were considered, with emphasis on anxiety, viewed as a drive state. This led to a consideration of neurophysiologic data bearing on anxiety, emotion, the sleep-waking continuum, and problems of consciousness. The role of the reticular activating system, as a widespread network of ascending influences upon cortical processes was considered, together with its possible implications for psychological and behavioral aspects of arousal, alerting, attention, and differential states of consciousness. Selected physiological indices of con-

[1] The survey of literature pertaining to this review was completed in July, 1954.

[2] The following abbreviations have been used in this chapter: EEG (electroencephalogram); P (persistent type alpha waves); M (minus type alpha waves); R (responsive type alpha waves); CFF (critical flicker frequency; CR (conditioned response); CS (conditioned stimuli); UCS (unconditioned stimuli).

ditioning, learning, and attentive states were discussed, as were also the effects of early life experiences on adult learning. Malmo highlighted the work of Delgado on the purposeful patterning of motor activities induced through electrical stimulation of the motor cortex. He concluded with a summary of experiments dealing with the production of behavior deviations and with psychosomatic disorders studied through the media of special procedures or recording techniques. These involved stress, conflict, and special clinical conditions.

The present review will begin with some theoretical publications which should be of interest to all behavioral scientists, but especially to neurophysiologists and psychologists faced with the problem of aligning the functions of the nervous system with behavior and psychological phenomena.

Theoretical Considerations of Brain and Neuron Organization and the Problem of Behavior

Electrophysiology, together with increasing knowledge of brain structure and chemistry, has provided neurophysiology not only with the working tools and methods, but with materials for fashioning testable hypotheses and for the development of new theories of brain function. But these gains in neurophysiology might go for naught, were it not also for the gradual, but systematic, accumulation of knowledge concerning behavior and its adaptations. Learning how we learn, whether by psychological, neurophysiological, biochemical, or other approaches, must be one of our main goals. With increasing knowledge of the finer structure of the central nervous system, and particularly with improved electrical means of tracing and plotting the course, magnitude, and temporal relations of events throughout the nervous system from receptors to effectors, there has come an increasing demand for comprehensive theories which, in part at least, will encompass the facts observed, but perhaps more importantly will serve to guide future research.

Among the things which have, in recent years, stimulated theorizing and considerable speculation, are the following: analogies and similarities between physical systems and living systems; cybernetics and theories of communication and control; analysis of properties built into machines such as digital and analogue computers designed to accomplish limited goals, but with high speed and effciency. The value of such theories and speculations is difficult to assess. Undoubtedly they inspire new ways of thinking about problems of brain function, but despite their neatness and attractiveness there still remains the fact that in last analysis it will be the facts of neurophysiology and of behavior which must determine the ultimate theory.

Eccles' (16) book is by far the most comprehensive, so far as a firm grounding in neurophysiological facts are concerned, but seems grossly attenuated and restricted on the behavioral side. He touches only briefly, and tangentially, upon learning and conditioned behavior. On the problem of "mind" he confines himself to a few brief pages on "will," perception, and conscious-

ness. Perhaps his neglect of behavioral and psychological data was intentional, but it need not have been for lack of data, for the literature is voluminous, some of it quite as quantitative and rigorous as any in the neurophysiological realm. Possibly because of his neglect of the behavioral side he was led to a kind of dualistic parallelism between mind and brain. Despite this criticism, it is an extremely important book factually and theoretically; the theory is detailed and specific, of the miniature-system, rather than molar-system, type.

Two recent books of quite different orientation are *Design for a Brain* by Ashby (3), and *The Living Brain* by Walter (66). Ashby poses the question, How does the brain produce adaptive behavior? Primarily from a consideration of behavioral data, he has attempted to deduce the properties the nervous system must have to behave both mechanistically and adaptively. His is a logicodeductive approach drawing upon observations of natural behavior and upon experimental animal studies. In an appendix he attempts expression of the relationships in mathematical form.

The seeming paradox of a brain at once mechanistic and adaptive, Ashby conceives of as a system which includes many variables, some of which perform as step-functions and others as part-functions. The whole is so assembled with a high degree of randomness that its detailed functions are of a statistical, rather than of a detailed, individual, nature. In order to account for behavior and its progressively selective adaptations or learning, he provides for a system which is both sensitive and adaptive within itself, so that accidental encounters with the environment leave their imprint permanently and widely distributed. Increasing numbers of encounters give rise to a statistical organization which leads to improved adaptation with each succeeding encounter. Ashby's position encompasses both an "evolutionary" or gene-pattern adaptation which leads to a kind of "natural selection" of behavior-patterns dependent upon inherited form and function, and a system of step- and part-functions which make possible better adaptation in the form of learned behavior.

His starting point is to rigorously define and establish "exact equivalences between the necessary physical, physiological and psychological concepts." This involves concepts of organization, behavior, behavior change, dynamic systems, systems including part- and step-functions, stability, adaptation as stability, and the principle of ultrastability.

The "principle of ultrastability" is the keynote of Ashby's argument. In his own words, "an ultrastable system acts selectively toward the fields of the main variables, rejecting those that lead the representative point of a field to a critical state but retaining those that do not." In essence this seems to mean that certain on-going processes of behavior, whether they be molar, as in the nature of the whole organism relative to its environment, or molecular, as in the case of a portion of the cerebral cortex, involve a field of variables shifted in one way or another to such an extent that they give rise

to critical states, which change the value of a step-function. With this change comes a modification in, and reorganization of the field of variables. Such reactions may occur again and again, but eventually a stable condition or state is attained.

When a step-function changes value the field of the main variables is changed, but fields differ in the relation of their lines of behavior to the critical states. Consequently with a distribution of initial states, and a distribution of critical states, a change in the field of variables will modify the proportion of points in the system which encounter critical states. Thus the process generated by change in step-function value, and change of field, is one of interaction such that field after field is rejected until one is retained. This is a process of field selectivity which goes on until a stable resting state is attained, or until the process is terminated, even though stability is not reached.

Some of these characteristics Ashby has been able to build into a mechanical model called the "Homeostat," but in addition he has been able to find examples of behavior of lower organisms, or learning in higher forms, which seem to exemplify the principle of ultrastability. Much more flexibility is required, however, than he was able to build into the "Homeostat," for it was designed as a fully-connected system, with all changes of variables being reflected in all others. Its selectivity of fields and its adaptation could not be gauged by degree; it either arrived at a terminal field or it didn't, and there was no gradation such as exists in animal or human learning. The response or adaptation was all-or-none. The behavior of a child in learning to walk, or of a novice in learning to drive a car, is characterized by progressive adaptation and change; there is "gradation." Also, as one system approaches its terminal field and adaptation, the changes in the other systems must not cause a loss in the adaptation of the first field. In other words, there must be "conservation" of adaptation gained. This is the essence of learning. Finally, with time, the number of systems adapted must not decrease; but they may increase or remain constant. Such "progression" in the systems is a requirement of learning.

Ashby believes that iterated, ultrastable, systems, which may arrive at stability or some terminal point independently, and may so do in sequence rather than simultaneously, will fill the necessary requirements stated above. The timing or delay from one state to another, the gradation, conservation, and progression are all necessary for learning, but so also is independence of systems, a serial adaptation, and interaction between adaptations. These more complex forms of learning and memory phenomena require additional complexity and speed among the systems of fields of variables involved. To account for this Ashby proposes the "multistable system," which consists of many iterated, ultrastable systems. Such a system will exhibit graduated adaptation, conservation of previous adaptations while new ones are being formed, and relatively rapid stabilization of its variables.

Ashby admits that some functions are unquestionably localized in the cortex, an example of which is the projection of retinal stimuli on the area striata. But what of the intervening association areas? Clinical and experimental evidence continues to suggest that fixed and localized circuitry cannot account for the effects of lesions of various types and locations upon learned behavior or the capacity to learn. Ashby believes that there is widespread dispersion of sensory impulses reaching the cortex and that these begin to pattern a map, including minute functional details which are determined at each synapse by factors of local significance and action. The local details, however, must persist, since learned behavior may be retained for years in the absence of disruptive factors.

A multistable system, consisting of many subsystems, would be expected to provide necessary dispersion of incoming information, since the sensory influx is variant, and no one set of variables will be consistently activated. The activity will spread and wander, but will eventually assume some degree of patterning through the operation of the principle of ultrastability. Thus despite dispersion and intermingling of subsystems, with attendant interaction and confusion with each new learning situation, there will still be selectivity toward useful interactions and rejections of unstabilized and competing ones. If interaction leads to nonadaptive behavior (critical states and unstabilized fields), this will in itself be cause for correction of step-function values which will break up this particular interaction. Then the new interactions resulting from new step-function values will be further tested against the environment. The process of forming and re-forming of interaction fields will stop only when a suitable set of step-functions has been found, which, acting upon the environment, provide behavior consistent with the keeping of essential variables within normal limits.

This functional-structuring of learning or adaptive patterns within the nervous system is meant to be flexible enough to encompass the many varied facts of the processes of conditioning, learning, retention, retroactive inhibition, and the like. In addition this logically deduced system of Ashby's is not inconsistent with some of the newer neurophysiological conceptions of cortical function. Ashby has confined himself to a logical and mathematical framework of rather broad dimensions which will fit many known facts of experimental behavior and learning, but he incorporates very little basic neurophysiology.

A recent publication by Cragg & Temperley (14) seems more adequately to provide the basic and causal properties of interaction among cortical neurons. On the basis of analogies from physics, involving ferromagnetism, they point out that atoms can interact and as a consequence of the interaction have different properties than in its absence. Similarly, it is pointed out that a large number of compass needles arranged in a lattice and moved closer and closer together, will begin to influence one another, and the influence will then spread to others in the lattice. All the compass needles in

this case may be referred to as an "assembly," but the pattern of local influence is called a "domain." It is this "principle of cooperative interaction" which guides their thinking relative to the organization of cortical neurons.

They draw upon facts of anatomy and neurophysiology to support their position. First, from an anatomical viewpoint it is known that neurons, like atoms, are numerous and densely packed. The "theory of cooperative processes" among neurons requires that they be capable of existing in two or more states of different energies. The presence or absence of an action potential is a well known condition neurophysiologically, which, provides two such energetic states. Furthermore, hypo- and hyperpolarization of cell bodies, dendrites, and *bouton termineaux*, in varying numbers and degrees, provide numerous additional states.

Interaction between neurons may be mediated by all-or-none impulses or by spread of current extracellularly from cell body to processes, and these in turn intertwine with many others. In view of these energetic states and structural arrangements among cortical neurons, it is quite possible to conceive of cellular interaction. Among large assemblies of cells, it is conceived that smaller "domains" would represent the "cooperative interactions," which would be constantly waxing and waning in size and constantly shifting direction and locus within the larger assembly. Thus one can have cooperative interactions among cells of a domain, or interactions among domains.

This is not unlike the conception of Ashby, which involves multistable systems composed of subsystems, each subject to the principle of ultrastability, which means constantly shifting fields and variables within fields, but always toward the goal of stability and adaptation. Likewise, Eccles' view is not dissimilar in principle, for in speaking of activity in the cortex and the way in which the discharge of impulses in a single neuron could, in 20 msec., give rise to excitation of hundreds of thousands of neurons, he states:

> Thus in general, the spatio-temporal pattern of activity would be determined not by two factors, but by three factors: (i) the micro-structure of the neural net and its functional properties; (ii) the afferent input; (iii) the postulated "field of extraneous influence."
>
> Elsewhere, he says, . . . minute "influences" thus exerted on a large population of neurones would be rapidly integrated in the form of a changed spatio-temporal pattern of activity in the neuronal net. There is thus in the active cortex a mechanism that could effectively amplify by thousands of times minute effects exerted on the individual synaptic knobs, provided of course, as postulated above, these influences have some "meaningful" pattern and are not random.

The differences in theory and point of view are less in the area of general principles and requirements than they are in the detail of how, when, and where, the changes come about. There are, however, similarities in each of these points of view.

Cragg & Temperley hold that any large assembly of cells would consist of a number of domains, each of which would be free to move through the assembly of neurons. Furthermore, each assembly would be divided into patterns of domains, each with different membrane potentials, which could be changed by incoming impulses, but would tend toward the statistical pattern most probable for the whole assembly, that is, the pattern giving the least total free-energy. Impulses arriving in a given area of cortex would be expected to change the energy level of the domains in the area, with the result that these domains might shift and move. By successive displacement of domains a "message" might thus be thought of as shifting from the sensory to the motor area in order to provide excitation and motor response. Such a learned pattern would doubtless be under the influence of domains throughout the cortex, since excitation in the domain of one area would be dependent upon the excitation levels of domains in other areas. Thus there could be close integration among various areas and domain patterns, without necessity of long and fixed circuits or neural pathways. A similar contingency was provided for in the model of Ashby, but was not dealt with in neurophysiological terms.

Cragg & Temperley make six deductions from their hypothesis of "cooperative interaction" among cortical neurons, and each of these is supported to some extent by anatomical, neurophysiological or behavioral observation. The deductions follow.

First, in the growth and development of nervous tissue there should be a sudden transition from a noncooperative to a cooperative assembly when fiber growth progresses sufficiently to initiate interaction between neurones. In support of this they cite the sudden onset and development of the electrocorticogram in embryonic and newborn animals first reported by Kornmueller (29), Jasper, Bridgman & Carmichael (23), and now confirmed by many others. Here, also, might well have been cited the onset of alpha waves over the sensory zones of young human infants, for the 3 to 4 per sec. forerunner of the alpha rhythm becomes persistent at about the age of three months. Corresponding with this, in a gross way at least, are the integrated perceptual acts which infants of three months are expected to perform on the Gesell developmental schedules. Also there are structural changes between birth, one month, and three months that Conel (13) has pointed out in his studies of the histology of various cortical areas, which correspond roughly with the onset of the electrical and behavioral changes.

The second deduction holds that an assembly of neurons will be composed of a pattern of domains and that an external disturbance, such as the arrival of an afferent discharge or electrical stimulation of a given area, will alter the whole pattern. This will not be restricted to a local primary response or even to single traveling waves, but instead will consist of varied and dynamic patterns of activity, like those demonstrated by Lilly & Cherry (37a), who recorded from large numbers of electrodes in close array on the cortex,

or like the toposcopic displays of human electroencephalograms by Walter (67).

The third deduction relates to the sizes and velocities of domains. They hold that it should be possible to predict the size of domains and the velocities of their boundary shifts in terms of the time-constant of the neurons and the overlapping of their processes. Both phylogenetically and ontogenetically, there is reason to believe that the range of dendritic ramification increases as one ascends the scale from mouse to man, or in the transition from birth to one or more years of age in the human infant. Conel (13), not only found greater length and ramification of dendrites from birth to one year of age in human infants, but he also found greater numbers of dendrites. Cragg & Temperley raise the question whether the greater interlocking of neurons with their greater length and ramification is a disadvantage or an advantage. From one point of view it might suggest that the periphery would have less discrete representation in the sensory and motor cortex; or if it makes boundaries travel faster, or reduces the size of domains so that the functional pattern contains more domains, it might suggest greater flexibility and speed of reaction.

In discussing the phylogeny and ontogeny of cortical development, it should be remembered that the frequency of the alpha waves increases along each scale; the rabbit has 5 per sec. waves, the cat 7 to 8, monkey 8 to 9, and man about 10. At three months of age the infant has 3 per sec. waves, at 1 yr. they are 5 to 6, and by 10 yr. they are usually of adult frequency, about 10 per sec. To what extent these changes in the temporal order of events in the cortex, as well as the changes in microstructure, condition the changes in perception, reactivity, and learning potentialities has not yet been determined. If such rhythms serve a scanning function, or are associated with an excitability cycle as Bartley (4), Chang (11), Bishop & Clare (9), Lindsley (39), and others have suggested, they may play a very significant role in the higher functions of the nervous system, a role which may govern the coding and timing of all varieties of integrations, including perception, learning, and motor response.

The fourth deduction maintains that, without afferent input, cooperative processes in isolated cortical tissue would develop a stationary pattern of domains, and there would be no detectable electrical potential. An applied stimulus would break up the pattern into smaller traveling domains with accompanying electrical disturbances. A stimulus supraliminal for all neurons would lead to homogeneity throughout the tissue, without traveling waves. The work of Burns (10) with isolated cortex tends to confirm these predictions.

A fifth deduction pertains to the effect of lesions. A region of damaged cortex would be unable to transmit domains, but should not prevent surrounding areas from forming domains and a functional pattern. Many clinical cases in the neurological literature are strongly suggestive of this arrange-

ment, and numerous ablation studies on rats, monkeys, and chimpanzees do likewise. The defects resulting from such lesions do not seem to have the characteristics expected by a circuit theory, but instead seem to be a function of the amount of tissue damaged rather than its locus, excepting of course lesions of primary sensory and motor areas.

The final deduction relates to the variability of response of individual cortical neurons studied by microelectrode technique. The number of discharges is variable from one stimulation to the next, a fact which is not consistent with a digital computer type of brain analogy, but is said to be in agreement with the cooperative type of analogy, for a neuron would fire when its locality was occupied by a domain of high excitation. Microelectrode studies have tended to show the discharge of single neuron spikes at a given phase of the underlying slow waves, which correspond in frequency to alpha waves and which seem to have an associated excitability cycle. These slower waves may represent domains of excitation and inhibition as alternate phases of their cycle. Whether they are standing waves or transient may depend on the state of the overall assembly of cells, or upon the patterns of domains represented, or upon the movement of individual domains.

Walter (66), in *The Living Brain*, treats of many things. It is obviously a general and popular treatise as the author intended. Among the topics are the following: electrical activity as a mirrow for the brain; significance of pattern in the brain's appreciation of its environment; the role of flicker stimulation in revealing the mechanism of perception; the role of mechanical models in helping conceive the integration of behavior; a convergence of viewpoints involving Pavlov's conditioning and Berger's electrocencephalgraphy with an analysis of the steps in learning; classifying personality through brain wave patterns; sleep, hypnosis, and miscellaneous topics; and finally speculations about the brain of tomorrow. This is a large order and, as might be expected, is a little like reaching in a grab-bag, for topics are developed in haphazard order, with little relation to basic neurophysiology, and at times involving little electroencephalography as well. But this is perhaps as Walter intended it, for his thinking is much more systematic in other sources (65).

The electroencephalogram (EEG) and its spatiotemporal elaboration known as the toposcope are described as a mirror for the brain. The toposcope, also better described elsewhere (68), is an array of some 22 cathode-ray tubes fed amplified EEG signals so as to present a kind of map of the fluctuating activity over the various surfaces of the head and brain. Frequency, phase and time relations may be obtained, but the pattern is mainly of interest, apparently, because of the patterns of flashing lights as different brain areas assume activity. The rate, sequence, and combination of flashed areas under various psychological and physiological states should provide some information relevant to the preceding theories of brain function. Perception, association, and learning are only a few of the conditions about

which the toposcope should provide clues, but apparently its patterns, like those of the brain it is said to mirror, are not easily understood. One should not expect the patterns of the brain's activity to be simple, whether revealed by introspection, overt behavior, psychoanalysis, or electroencephalography.

Walter (66) discusses the effects of flicker, both in the EEG[2] and in the subjective reports of subjects so exposed. From flicker he goes to a brief statement of his scanning theory of the alpha rhythm, more completely described elsewhere (64). In this conception the alpha rhythm is a process of scanning or searching for a pattern, which subsides when the pattern is found. He believes that alpha scanning will serve other sense modalities as well as vision. In order to answer a question in brain physiology, according to Walter, he posed the question, " . . . whether the elaboration of cerebral functions may possibly derive not so much from the number of its units, as from the *richness of their interconnection*." To test this hypothesis he built a mechanical model called *Machina Speculatrix*, attempting to incorporate into it animal-like characteristics of exploration, curiosity, goal-seeking, self-regulation, memory, learning, form recognition, and the like. The number of units corresponding to nerve cells was two and there were two corresponding receptor organs, a photocell for vision and an electric contact for a tactual receptor. When its batteries are charged it is continually active, seeking, and exploring. It is endowed with a positive tropism which attracts it to lights of moderate intensity, but is repelled by bright lights. Its visual scanning mechanism is linked with the steering mechanism so that it goes in the direction in which it is attracted by appropriate light intensity. Several other characteristics were included in its repertoire of responses. Whether such models are any more than toys seems at this point debatable. One of the major accomplishments of the book is an analysis of the learning process, which he outlines in two steps: the selective operations of differentiation, extension, mixing, and summation, plus the constructive operations of activation, preservation, and combination. The result is a conditioned response.

In one section of Walter's book he attempts to relate the EEG to personality characteristics. Like the alpha rhythm scans for visual sensory stimuli, he speaks of the theta rhythm scanning for pleasure. The theta rhythm is a 5 to 7 per sec. activity found over the central and frontal regions of the head and over the temporal region in aggressive psychopaths, delinquent and behavior problem children, and in normal individuals during frustration. To further analyze the alpha rhythm relative to personality and temperament, he resorts to a segregation of patterns according to whether the alpha rhythm is persistent, responsive, or minus where little or no rhythm is present. The small and somewhat rare group of individuals with P-type[2] alpha waves is said to include mainly those who are abstract thinkers and persons who do not think in terms of visual images. The M-type[2] person is pictured as having rapid and precise performance, but is a person who tends to block on problems of abstract nature. The R-type[2] or responsive

group consists of people whose alpha blocks readily to stimulation, and who in personality characteristics are intermediate between the other two types. The obvious differences in EEG patterns strongly suggest some kind of characteristic difference in the make up and functioning of the brain, but it is not yet clear whether this could be personality. If so, it must have a strong genetic and constitutional flavor, since the EEG pattern seems to be to a large extent an inherited pattern. It tends to remain relatively fixed throughout life except during the early years, and perhaps the senescent years.

Enthusiasms over cybernetics, communication theory, and control devices and attempts to find analogies between physical and brain processes, have led to a good deal of theorizing and perhaps even more speculation. Analogies between brain and machine have been discussed by MacKay (42). The immediacy of the practical application of one means of transducing and transmitting visual images electronically and their reinstatement for remote perception by means of the television scanning process, has given rise to an analogy between the scanning raster of the television screen and the alpha rhythm of the brain, especially as it may apply to visual perception. The synchrony, timing, and repetition rate of the former is such that intensity modulations of the trace in successive lines of the scanning raster give rise to definitive images. That the 10 per sec. alpha rhythm of the brain might serve a similar scanning function was first systematically put forth by Pitts & McCulloch (54). They developed a concept of nerve-net models employing neurophysiologic principles and utilizing histologic knowledge of the structure of the cortex, insofar as possible. Their schemata included a representation of nerve-nets arranged in layers corresponding to the traditional six-layered cortex, and their theory provided for the alpha rhythm to so move through this network as to make possible coincidence of excitable periods with the influx of sensory impulses. At the same time this arrangement was postulated to preserve the necessary spatiotemporal characteristics to account for size-constancy phenomena or what McCulloch later described as the knowing of universals (a triangle is a triangle regardless of size or orientation of the projected image). Furthermore, they felt that the time characteristics of the alpha rhythm (10 per sec.) were such that the limitations imposed by it corresponded in general to those traditionally observed with respect to serial perceptual scanning efficiency.

From the foregoing discussion of theories, it will be apparent that there are among them disparities and incongruities, which is to be expected because they have been inspired by different points of view and emphasis. Some have arisen because of a need to integrate rapidly accumulating neurophysiological data, others from a need to find in the structure and function of the brain an explanation for natural phenomena experienced and behavioral data. From experimental studies of discrimination, learning, and retention in animals, especially studies involving ablation of various portions of the cerebrum, there has come a need to explain results which seem to

defy a concept of localization of such functions, or of an atomistic, engrammic representation in specific neural pathways or circuits. Likewise, the clinical observation of patients with naturally-occurring or surgically-produced lesions raises serious doubt about specificity of representation of various higher functions of the nervous system.

Electrophysiology, developing from the point of view of the individual nerve cell and its processes, and gradually extending to the more centrally located aggregates of cells involving different structures and complicated interrelationships, has found it difficult to explain central electrophysiologic phenomena. Electroencephalography, representing a gross and molar overview of certain cortical electrical manifestations, some of which have shown unique diagnostic potentialities, has opened a new realm of speculation about brain function, which at times seems to conflict with the more atomistic or molecular conceptions of traditional neurophysiology. The latter has supplied much of the necessary information about basic properties of nerve tissue, such as irritability and conductivity, and has, in fact, traced the course of nerve impulses from their origin in receptors to the brain and from the brain to their destination in effectors. Although progress is being made, the communication lines are essentially lost within the brain; certainly what happens in the complex matrix of the cortex is still an enigma. Presumably, similar basic properties of neurons are retained, but the extent to which additional and modifying properties are introduced by tremendous aggregates of nerve cells in the brain remains to be determined.

The discovery of rhythmic, autonomous, potentials, especially the well-known alpha waves of the human EEG, has given rise to varied conceptions of their origin, meaning, and significance for brain function. One of the earliest and most basic of these was the observation made by Bishop (8) that the alpha wave has an associated excitability cycle which permits impulses to be effective at one phase and not another. This notion is fundamental to others such as the various conceptions of the alpha as a scanning device. However, the excitability concept may exist without the scanning notion.

Experiments Bearing on Excitability and Scanning Role of Alpha Rhythm in Relation to Behavior and Psychological Processes

Perceptual experiments.—As a test of the hypothesis that the alpha rhythm serves as a scanning mechanism in the control of perception, MacKay (43) arranged for spiral rectangular or triangular figures to appear on a large cathode-ray screen with increasing or decreasing size at varying rates determined by the experimenter. The object was to determine whether at certain frequencies, ranging from 2 to 30 per sec., but with particular emphasis on the 9 to 11 per sec. alpha frequency range, there would be anomalies or discontinuities in visual perception. No stroboscopic effects were noted by several different observers. In another experiment a phase-correlator was

used to determine whether there were phase relationships between the growth of the perceptual object and the alpha waves. Again no significant correlations were found, even when the EEG was used as a feedback to control the brightness of the figure. MacKay concluded that although the results do not disprove the scanning hypothesis they limit considerably the possible role of the alpha rhythm in such speculations. He states that scanning in the sense in which the engineer uses the concept may not be necessary and that,

> Invariance with respect to size can be secured merely by a statistical coupling (formed as a result of experience) from a sufficient number of states of excitation representing equivalent patterns of different size, to the response pattern found in experience to be a satisfactory adaptation to that invariant

[MacKay (1951, 1952)]. This concept is similar to that proposed by Ashby for the fixation and consolidation of learning processes and presumably for the recognition thereof.

Murphree (52) has attempted to test some of the implications of an alpha scanning mechanism for perceptual processes. On the hypothesis that the alpha rhythm is an index of the processes which limit the speed of rapid successive form perceptions, and that apparent motion is a partial failure in these processes, he has deduced the following corollaries. Separate form images may not be perceived at a rate faster than the alpha rhythm; differing forms presented successively at rates faster than alpha frequency will be perceived as in motion or in simultaneous existence, depending on the ratio of their rate of presentation to the alpha frequency; the rate of form presentation at which apparent motion ceases (threshold of simultaneity) will be proportionate to alpha frequency; the maximum rate at which separate images can be perceived will be proportionate to alpha frequency; and segments of a composite form presented separately at or above alpha frequency will be seen as a composite form. He also investigated the reversals of figure-ground effects to determine whether alpha frequency was in some way related to the reversals. Fifty subjects were selected whose alpha frequencies ranged from 8 to 13 per sec. They were then tested for their threshold of perception (exposures per second) on each of the tasks. The exposure apparatus consisted of a viewing box and a hole in a screen through which portions of a rotating disc could be seen with each flash of a photoflash tube activated by commutators on the shaft of the disc. In effect it produced successive tachistoscopic exposures.

The results demonstrate that the relation between alpha frequency and the exposures per second for each of the different performances tends to be similar. The relationship is curvilinear, with the lowest threshold for subjects with an alpha frequency of about 10.5, and higher values for subjects with frequencies on either side of the central tendency for alpha range. Murphree finds that the best fit of his curves is described by a first-order equation:

P equals K plus absolute alpha frequency minus 10.3, where P is performance or events per second at which perceptual threshold occurred, and K equals a constant of a particular value for each type of performance. He thinks the 10.3 may represent the mean value of some other process, perhaps in the retina. He concludes

> that there is a significant relation between the alpha rhythm and the temporal aspect of rapid successive spatial perceptions,

and that

> strong support is indicated for the view that maximum rates of form perception, apparent motion, figure-ground reversals (at appropriate rates) and fusion of separate spatial elements into composite forms are mediated by a nerve net of which the alpha rhythm is an integral part.

Perhaps of greater significance for alpha scanning or excitability hypotheses is that fact that the mean span of simultaneity, or the maximal temporal interval between two events which are perceived as simultaneous, was .095 sec. and the mean duration of alpha cycles was .098 sec.

That there is not a direct linear relationship between alpha frequency and exposures per second for the different perceptual processes studied raises some doubt about the support that this study gives a scanning hypothesis. However, the threshold for simultaneity tends in this direction and its mean span corresponds to the mean alpha frequency for the group. It is of interest further, that the group of subjects with a mean alpha frequency of 10.5 per sec. has the lowest threshold for each of the perceptual tasks and that this value is the approximate mean alpha frequency for adult subjects generally. Additional studies of this type are needed, particularly those in which the alpha frequency is monitored at the time of the perceptual tests to insure a more accurate frequency appraisal at the time the judgment is made.

Walsh (62) presented, tachistoscopically, 1 to 10 luminous dots in patterned array to subjects reclining in darkness and fixating a small red light. He found that the ability of his subjects to recognize patterns did not depend upon the amplitude of the alpha rhythm. This, however, is not a disproof of the alpha scanning or excitability hypotheses, if one assumes that the recorded alpha rhythm does not necessarily represent the alpha activity, which may exist in aggregates of cells concerned with the particular perceptual process. Actually, the field from which alpha is recorded in the EEG may not be homogeneous in this respect. Maximal alpha voltage is probably a function of the degree of homogeneity, but minimal voltage or absence of alpha in the EEG record need not imply that alpha activity does not exist in smaller fractions of the total field of neurones, each with a basic 10 per sec. beat but of different phase relations, thus giving rise to desynchronization in the externally recorded EEG. The alpha rhythm is only a general index of the state of synchrony in the field. Microelectrode studies give some support to this belief.

In another part of Walsh's study subjects were exposed alternately to trains of clicks and flashes, but the amplitude of the alpha waves did not differ significantly under the two conditions. Walsh interprets this as failing to support Adrian's (1) view that the alpha rhythm, which he believed to originate in the visual field, may allow one to concentrate one's attention upon other than visual afferent stimuli, whereas in its absence visual attention is in process. Presumably, for Walsh's results to support this concept, he should have found alpha waves waning during visual counting and waxing during auditory counting. Instead, he found them similar under the two conditions. It is generally observed that any new or unexpected stimulus is capable of producing a momentary blocking of alpha waves, but in many subjects after adaptation to a pattern of repetitive presentations, even visual stimuli will be relatively ineffectual in interrupting the alpha rhythm. A slight change in the pattern or intensity, of the stimuli will often reinstate the alpha blocking. That visual and auditory stimuli interact has been demonstrated by Torres & Marshall (60), using a cathode ray oscilloscope superimposition method developed and described by Dawson (15) to bring out minimal evoked potentials, which because of their constant relationship to regular stimuli stand out in a record otherwise dominated by spontaneous electrical activity.

Mundy-Castle (50) attempted to determine the relation between alpha frequency and visual perception rate by presenting three types of material tachistoscopically. Fifty-four subjects were exposed tachistoscopically to cards with circles for a measure of "span of apprehension," circles containing letters for "span and memory," and complex nongeometric figures to be identified and matched ("recognition"). Only two significant correlations were obtained: higher alpha frequency was associated with highest number of complex figures perceived and with highest number subsequently recognized. Apprehension span, and span plus memory for letters, were not significantly correlated with alpha frequency. He concludes that the finding of two significant positive correlations between alpha frequency and rate of visual perception provides some support for the alpha scanning theory. He was also impressed with the finding that low CFF[2] is associated with low alpha frequency, and high CFF with high alpha frequency. The correlation was of the order of .545.

A variety of phenomena are seen during increasing visual flicker frequency, especially at the lower frequencies. There may be subjective color, movement, and geometric designs. All colors may occur, but red, yellow, and orange are most common according to Gastaut (17). Movement may occur in spirals and may change direction but not in accord with the scanning hypothesis for it is unrelated to shifts toward or away from 10 per sec. flicker. The perceptions are unstable and shift without warning to other patterns. Walsh (63) offers an explanation for the visual pattern illusions which is not unlike the theory of ultrastability proposed by Ashby. He holds

that the brain compares arriving patterns of impulses with those previously received in normal experience. Because no good fit occurs, the brain rejects each successive comparison, thus giving rise to instability and shifting of patterns with the resulting illusions.

Other illusory phenomena of flickering light have been reported by Bartley (5), and have been discussed by Lindsley relative to the alpha excitability hypothesis (39). One of these is the brightness enhancement, or Bartley effect, where the subjective brightness of a flickering light is supposed to appear very much brighter at frequencies in the alpha range than at either lower or higher frequencies. The second phenomenon is the subjective impression of two lights, successively, where only a single flash has been presented, providing the intensity and duration are appropriate. The duration in such instances is of the order of 50 to 100 msec. which would stretch over the duration of two alpha peaks or in terms of the excitability notion, would cover two excitable points separated by an inexcitable period. According to the excitability concept, the influx of impulses would therefore be disrupted at the cortex by the waxing and waning excitability associated with the alpha rhythm.

Psychomotor phenomena.—Still other types of experiments bear upon the hypotheses of alpha scanning mechanisms and the association of an excitability cycle with the alpha activity. Walsh (63) studied visual reaction time in relation to the alpha rhythm with the view of testing the alpha scanning hypothesis. The following results were obtained: (*a*) reaction time did not vary significantly when the stimulus fell during the presence or absence of occipital alpha activity; (*b*) no significant correlations were obtained between reaction time and amplitude of alpha waves; (*c*) no significant differences in reaction time were found when the stimulus fell during different phases of the alpha cycle; (*d*) with stimuli reduced to near threshold value the effect of the amplitude and phase of alpha waves at the time of stimulation was evaluated—only chance relationships were found. Walsh's results therefore suggest that the variations in visual reaction time cannot be accounted for in terms of a scanning hypothesis, which postulates delays occasioned by unreceptive or inexcitable phases.

A more extensive and better controlled study has been done by Lansing (30), in which both occipital and motor alpha rhythms were recorded along with finger tremors of the responding finger. Thus the onset of the stimulus light and the finger response bounded the reaction time, and both the stimulus onset and the beginning of the response could be studied in relation to the phase, frequency, amplitude, and other conditions of the occipital and motor alpha rhythms and tremor rhythms. It was found that the longest reaction times occurred when the stimulus fell in one particular part of the alpha cycle. It was possible to delineate phases of the alpha cycle, which, for all subjects, tended to produce shorter or longer reaction times. Since this was the point at which the stimulus fell, the phase-region on the alpha cycle

was corrected for the retinocortical latency (about 30 msec.) and moved farther along on the cycle. Likewise, the point on the motor alpha cycle at which the response occurred was corrected for latency (about 15 msec.) from motor cortex to muscle response and moved back by a corresponding amount. After these corrections were made it was found that the excitable phase of the occipital and motor alpha waves corresponded. They were, however, separated in time by 75 to 100 msec., the apparent delay in transmission from occipital to motor cortex. The amount of delay corresponds roughly with the duration of an alpha cycle, thus permitting the excitable phases to coincide.

Frequency and amplitude of alpha rhythm at the time of stimulation bore no significant relationship to reaction time. This result confirms the findings of Walsh (63) and O'Hare (53). The motor response tended to occur on the same phase of the motor alpha cycle, and also on the descending phase of the finger tremor cycle. Although there is often close similarity between the motor area alpha rhythm and the finger tremor rhythm with respect to frequency, there are at times both slower and faster tremor components which do not correspond, and the phase relations of the two, even when of similar frequency, do not maintain a constant relationship. This similarity, but lack of perfect agreement, has been observed previously by Jasper & Andrews (22). They felt the tremor rhythm might be a product of the influence of the basal ganglia and the motor cortex.

A study not necessarily pertinent to the scanning or excitability hypotheses is one in which the relationship between reaction time and alpha blocking time was investigated by Stamm (59). He introduced certain experimental conditions which reduced reaction times systematically, but found that the alpha blocking time did not show a corresponding reduction. The correlation between reaction time and alpha blocking time was about .30. The alpha blockings usually occurred after the reaction, but sometimes occurred before. Stamm concluded that the two measures, though related to some extent, are essentially measures of different systems. Since alpha blocking time is usually longer than the overall reaction time, the latter can hardly be dependent upon the former.

Kibbler *et al.* (26), recording the EEG simultaneously with measures of eye opening and other voluntary movements, found a definite correspondence between the time of initiation of the movement and a given phase of the alpha cycle. Likewise, Bates (6), comparing finger movements with phase of the alpha cycle, found a definite relationship indicative of a controlling influence.

Meister (46), who brought together much of the information which might be interpreted as supporting a scanning hypothesis, has also studied saccadic eye movements in relation to the phase of the alpha rhythm. He found significant relationships between the phase of the alpha and the beginning of eye movements. He proposed a "neuronic shutter" mechanism to account

for the clarity and lack of smearing of visual impressions while making successive fixations as in reading or in voluntary tracking with the eyes. In contrast, movement of the eyeball by lateral pressure, or during involuntary movements induced by vestibular or brain stem reflex, tends to cause smearing of the images in the visual field.

The "neuronic shutter" concept, analogous to the shutter mechanism on a film projector, is conceived as an alpha scanning device with excitability periods attuned to eye movements, so that successive impressions arrive in discrete rather than continuous array. These and other examples of psychological phenomena, which may be interpreted in the light of an alpha excitability cycle, have been brought together, with supporting data from neurophysiology, by Lindsley (39).

The scanning and excitability concepts may exist in combination, and the former depends upon the latter, but the reverse is not necessarily the case. Bishop (8) must be credited with the excitability cycle notion, and Bishop has consistently found evidence for it on neurophysiologic grounds. Chang (12) has also provided interesting neurophysiologic support for excitability cycles comparable to the alpha wave duration, and also for both shorter and longer excitation cycles.

Recent microelectrode studies (2, 7, 25, 37) of unitary responses in single cortical cells indicate two types of activiy, slower potentials of the order of spontaneous activity such as the alpha, and spike discharges. Li, McLennan & Jasper (36, 37) hold that the slow waves are not the result of envelopes of spike discharges nor are they due to nerve impulses in self-re-exciting chains. They suggest that the slower potentials may be due to membrane potentials. This would seemingly make possible a role associated with excitability of individual units and also aggregates of units. Although not uniformly found, there is a tendency for spike discharges to occur on a given slope of the slow waves, suggesting an excitable phase.

Mental imagery and the EEG.—An attempt has been made in some recent studies to develop objective measures as substitutes for introspection in the investigation of imagery and patterning within the brain. Short (57) used measures of respiration and the electroencephalogram to correlate with imagery-type. He found significant correlations between physiological-type (respiration pattern and EEG pattern) and imagery-type. For example, visualists tend to breathe regularly and have M-type alpha rhythms (M-represents Minus, or very little alpha); verbalists tend to breathe irregularly and have P-type alpha rhythms (P stands for Persistent alpha not readily disrupted); the R-type alpha pattern (R stands for Responsive, that is, alpha easily blocked by stimulation) individuals are visualists or verbalists depending upon whether they are regular or irregular breathers.

Short & Walter (58) have extended this type of investigation to include imagery and the motor elements of thinking. In a psychophysiological study of imagery through the kinesthetic-tactual modality (stereognosis) they

have asked adults and children to trace patterns of grooves imbedded in cement blocks with one hand and to attempt to reproduce the pattern in a drawing with the other hand. The problem also involves the perception or meaning of the letter, figure, or object represented. They employed measures of respiration, muscle tension, electroencephalogram, and the position of the hands by means of a new electrostatic limb position indicator. The results indicate that M- and P-type alpha subjects not only produce more correct answers but do so in a shorter exploration time than do the R-type alpha subjects. The success of the M- and P-types in stereognosis depends mainly upon their consistency in the use of one type of imagery, visual for the Ms, and verbal for the Ps. The Rs tend to vacillate in their imagery from visual to verbal. They also show frequent and irregular bursts of alpha rhythm, mixed respiratory patterns, and lack of movement-correspondence between feeling and drawing with the two hands. Persons of the R-type alpha activity, and kinesthetically oriented, are often given to gesturing, and tend to be "limp" and relaxed when their hands are moved to the starting position in the task. On the other hand, visualists and verbalists, or the M- and P-type alpha subjects, are more tense and less easily manipulated. The unsuccessful perception of the pattern traced is said to be linked to a variable use of different types of imagery, and also to fluctuation of the alpha rhythm and its partial blocking.

These observations are like many others which have been established empirically with respect to the EEG; they are reproducible and valid, but our lack of knowledge about the origin of the EEG and the basic properties of the cellular matrix from which it arises, does not yet permit us to understand fully what the correlations mean. Is it possible that tactual-kinesthetic clues constituting the principal source of sensory input from this task reach the common sensory zones, there to spread and link up with the predominant mode of past experience, whether it be occipital lobe in the case of visualists, or temporal lobe in the case of verbalists? If the spread of change initiated in the primary sensory zones is to the occipital it will find a condition of low alpha or a relatively desynchronized EEG (M-type, visualist), but one readily receptive because its alpha activity exists in numerous aggregates of cells any one of which may participate if its phase is right to provide an excitatory state when the spreading change arrives. This makes for speedy processing of incoming information, since there is always a group of cells whose phase relation, and therefore excitability, is appropriate for response. If the spread has been conditioned by many previous experiences toward the temporal lobe, and therefore auditory and verbal imagery, such will result, but the occipital alpha may remain high and unimpaired (P-type, verbalist). The fluctuation of these two tendencies, as in the case of a man in a state of indecision, leads to confusion and lengthening of response time. In this instance the EEG pattern according to Short & Walter tends to show a fluctuating alpha pattern (R-type, mixed or alternating imagery).

The question then arises, (*a*) are the alpha patterns genetically determined, and therefore one's mode of imagery essentially predetermined, or (*b*) does experience gradually establish the mode of imaging and perceiving. The latter could come about through processes similar to Ashby's "principle of ultrastability" and the interaction of fields of variables, or through Cragg & Temperley's "cooperative processes" with the formation of domains, and assemblies of domains. If one assumes a measure of randomness in the degree of exposure to one or another type of stimulation in the environment over a period of time, then statistical probability would favor a mixture or balance of tendencies and the development of an R-type alpha pattern with mixed imagery. This would seem to be borne out by the distribution of R-, M-, and P-types of alpha patterns found in the population at large. According to Walter (66), about two-thirds of the ordinary normal group selected at random are found to have the R-type, and the remaining third is about evenly divided between M- and P-types. Undue emphasis upon one or another type of experience, whether visual, auditory, or tactual-kinesthetic, from early infancy on could no doubt swing the balance in favor of M- or P-types, and constant reinforcement of the predominant modality would favor that type of EEG pattern and imagery. Would the infant and child who is cuddled and fondled and talked to extensively by the mother become a verbalist by virtue of the tactual-kinesthetic and auditory predominance of stimulation? Would the child who has a minimum of attention be overwhelmed by the visual world of things, in lieu of the relative deficiency of other types of stimulation, and become a visualist, predominantly? Obviously there would be many cross-currents of influence through the medium of rewards, penalties, and reinforcements. We hear much about the effects of differential treatment of children from early infancy on, especially with regard to their affectional needs, and the dire consequences if there has been too much or too little love and attention. The balance of influence in this regard is no doubt an important determinant of the activating properties of drive and motivation. These in turn must inevitably relate to and influence and be influenced by the predominant modes of perceiving, imaging, thinking, and acting.

But to return for a moment to the opposite point of view. To what extent are the alpha patterns determined by heredity? Identical twins tend to have very similar patterns, more so than ordinary siblings (34, 35, 55), and parents of epileptics are reported to show more dysrhythemia of a similar type than parents of nonepileptics (32, 33, 41). On the other hand, the differences in EEG patterns become more obvious during adolescence and in adulthood than they are during infancy and early childhood. Also, even among adults where waking patterns may differ very markedly (M-, P- and R-types), it was reported by Knott *et al.* (28), in studies of individual differences during waking and sleeping, that sleeping EEG patterns become more homogeneous, and, in particular, Henry (19, 20) observed that the initial waking patterns

after a night's sleep were much more similar for all individuals than when well into the day's activities. It was concluded that environmental factors, as well as inborn characteristics may determine the amount of alpha activity in the EEG. These and other results along this line were discussed by Lindsley (38, p. 1045–49) in a review of the subject ten years ago. The association of perceptual mode and imagery type with EEG patterns in recent research seems important and may hold real promise for future lines of investigation, inasmuch as direct and objective approaches to perception and imagery appear to be available. Attempts to associate the EEG with the grosser aspects of personality which are less well defined and less amenable to measurement have met with little success. Perhaps in this way better concepts of temperament and personality will be attained.

Mundy-Castle *et al.* (51) compared the EEG's of African adults and European adults and found no gross differences. Because of the wide differences in race, culture, and society represented in the two groups they concluded that, although a few minor aspects of the EEG may be linked to cultural differences, the main determinants of the EEG are on a hereditoconstitutional basis. There was some indication of a more persistent (P-type) alpha pattern and less beta activity among the natives than among Europeans and, in general, a more anterior or centrally located origin of alpha activity.

Elsewhere, Mundy-Castle (50) has attempted to relate the EEG to temperament defined as "that group of hereditoconstitutional factors which characterizes on individual's mode of reaction to his environment, and which forms the basis for the development of his personality." The orientation is the Heymans-Wiersma-Biesheuvel temperament theory, which incorporates the following factors: primary-secondary function, emotionality, and activity. "The *primary function* of any conscious mental event is its immediate experience, its *secondary function* the after-effect it is capable of exerting after receding from consciousness." Subjects can be rated to the extent that their behavior is influenced by secondary functioning. Those influenced by primary function are said to be quick, impulsive, and variable; those influenced by secondary function are cautious, steady, and perseverative. "Emotionality" refers to the stimulability of the autonomic nervous system and tends to determine the strength and prevalence of autonomic reactions. Emotionality is implied to give behavior warmth and emotional tone. "Activity" refers to the frequency and strength of an individual's reactions in proportion to motivation. A possible fourth factor, called "emotional instability," but unlike the others in not being continuously distributed, may be involved in emotional behavior.

Using a variety of measures of "psychic tempo" (tapping, walking, writing, talking, adding, etc., speed tests) to evaluate secondary function, in addition to ratings, Mundy-Castle found that the ratings correlated significantly with alpha frequency and that several of the speed tests did also. He also found an association between alpha frequency and the predominant

phase in manic-depressive psychosis; the manic-phase patients are considered to be "primary-functioning" and have high alpha frequencies, whereas the depressed manics are considered "secondary-functioning" and have lower alpha frequencies. There was a significant correlation between alpha frequency and critical flicker fusion frequency, which was considered important because both measures are related to secondary functioning and have lowered values, whereas as in primary functioning individuals the alpha frequency and CFF are higher. In his extensive study Mundy-Castle assumes the alpha rhythm has a scanning function and that it is associated with an excitability factor. Frequency of the alpha rhythm, or the scanning function, has been his most important correlate with other factors involving speed—of perception, tapping, talking, and the like. These characteristics tend to be found in the "primary functioning," quick, impulsive individual, whereas lower frequency alpha and psychic tempo functions tend to be found in the "secondary functioning" individual.

Conditioning and the EEG.—The electroencephalogram has been used as an index of conditioning by a number of investigators in the past (24, 27, 40, 48, 49, 56, 61). The basis for this has been the fact that auditory or tactual stimuli, after a few repetitions ("adaptation"), do not produce a blocking of the occipital alpha rhythm. Visual stimuli are much more persistent in this respect. Consequently, auditory or tactual stimuli have been used as conditioned stimuli (CS) and visual stimuli have served as unconditioned stimuli (UCS). Alpha blocking is the original unconditioned response (UCR) and becomes the conditioned response (CR) after several pairings of the CS with the UCS. Jasper & Shagass (24) demonstrated a variety of conditioned reflex phenomena in man, including simple, cyclic, delayed, trace, differential, differential delayed, and backward CR's. The studies of Travis & Egan (61), and Knott & Henry (27) raised questions as to whether conditioning produced in this way was "true" conditioning or merely a kind of "sensitization" phenomenon, since the CR[2] did not increase consistently during the pairing process. Whatever the process involved, it has generally been recognized that a stimulus originally ineffective in producing alpha blocking (sound, after adaptation) when paired with an effective agent (light) will come to produce blocking of the alpha rhythm. It is not a particularly stable response.

Among recent studies may be mentioned the work of Motokawa's laboratory in Japan. Motokawa & Huzimori (49), in studying the acquisition of a conditioned galvanic skin response, also recorded the EEG. A bell served as CS[2] and an electric shock as UCS.[2] They observed three types of changes in the EEG record during the course of conditioning, and these actually exhibited conditioning before the galvanic skin response. These were (*a*) an alpha blocking, (*b*) beta wave augmentation, and (*c*) baseline deflections of irregular character. The increase in fast or beta waves, and the alpha desynchronization are similar to the effect of stimulating the ascending reticular formation which produces the so-called "activation response" (44).

Not only did the potential changes in alpha and beta waves, which they called excitation potential (Ep), occur earlier than the galvanic skin response but it was more resistant to extinction. Of special interest is the fact that during extinction the alpha rhythm appeared stronger than before, whereas during spontaneous disinhibition an excitation pattern occurred. Consequently they believe that a strong alpha rhythm is consistent with a cortical state of inhibition.

Motokawa (48) observed that the cortical conditioned response (Ep) not only occurred before the peripheral response (galvanic skin response) but that it is more flexible and subject to differential conditioning. Iwama (21) established delayed conditioning using a metronome as a CS, and alpha blocking as the CR. The delay interval was 20 sec. He reported an augmentation of the alpha rhythm with the onset of the metronome (CS) and a blocking of alpha and beta activity toward the end of the delay period. The alpha increment with the CS he interpreted as the result of internal inhibition. A beta wave pattern, in response to extraneous stimuli introduced during the delay period, he interpreted as disinhibition. Following extinction, it was observed that alpha waves were strong, and this was interpreted as extinctive inhibition.

Morrell & Ross (47), following the concepts of Pavlov, assumed that extinction would leave a process of inhibition in the cortex and that this would interfere with the operation of another response system associated with the conditioning process. Accordingly they used a low tone or buzzer as a CS, and a flickering light as UCS, and the CR was the blocking of the alpha rhythm. As the pairing of the CS and UCS was repeated the CR occurred. Associated with this was an instruction to the subject to respond to the light stimulus by pressing a key. This provided a reaction time measure against which to gauge the effects of cortical inhibition, the assumption being that reaction time would increase when this response mechanism, which had been consistently linked with the conditioning process, was affected by the inhibition associated with extinction.

They believed they were able to demonstrate that the reaction time during the period of no alpha block to sound, and during the subsequent pairing of sound with light to produce conditioning, was of the order of .3 sec., whereas, as the extinction was taking place the reaction time increased to .6 or .8 sec. The increase in reaction time was interpreted as a result of cortical inhibition which influenced the transmission from occipital to motor cortex. It was assumed that retinocortical transmission time and motor cortex to response time were constant and that the total reaction time could be used as a measure of central transmission time. To demonstrate differential inhibition they conditioned alpha block to a specific stimulus and after the CR was established suddenly introduced a new stimulus which also blocked the alpha (Pavlovian generalization). Thereafter by reinforcing only the first sound with light, the second sound eventually does not produce alpha blocking

(differentiation). This state of differential inhibition to the second stimulus was then tested for the effect that it might have upon the reaction time and again it was found that reaction time to the light was increased from .3 to .8 sec. The same lengthening of reaction time was demonstrated during delayed inhibition.

This approach for dealing with cortical states of excitation or inhibition set up by one process as they may affect another process is an interesting one, but it is in need of very careful evaluation and control. To imply that processes may exist side by side with varying amounts of overlapping, depending upon the order in which the stimuli occur, the nature of the instructions given, and various other factors, may be logical enough, but (at least in a human study such as this one) it seems to neglect a good many factors requiring careful control. For example, the light which served as UCS always had to be given in association with the CS in order to have a test of reaction time. The subject may have become adjusted to not seeing the light during several CS-only trials and simply was not ready to make a response when it reappeared without warning, thus lengthening his reaction time. Likewise, the presence of the finger reaction at one time and not another gives rise to differential stimulus input, which is not taken into account.

It will be evident from the foregoing experiments that some progress is being made in developing new approaches to higher mental functions. For many years, they have resisted objective study and have been dependent upon introspection, which in many instances may be unreliable or unconvincing. Pavlov gave us a methodology for investigating one type of learning and, in addition, was able to demonstrate numerous behavioral principles of far reaching significance. He speculated about the nature of central nervous system control of conditioned reflexes and restricted conditioning to the cerebral cortex, developing concepts of excitation, inhibition, irradiation, and the like. Berger in 1929 discovered cortical rhythms recordable through scalp and skull, which have to this day defied interpretation. This phenomenon constituted a strong inspiration to many workers because it gave a new parameter of measurement and a new approach to the brain. The extent to which cortical rhythms, and especially the alpha rhythm, are involved in many of the recent theoretical and speculative accounts of brain function is an indication of Berger's influence in discovering and identifying the EEG. Many subsequent EEG studies, both clinical and experimental, during the past 25 years have added in one way or another to bring us closer to a resolution of how the brain serves the function of the mind.

It seems particularly significant just now, with the progress of electroencephalography, but more particularly the advances in neurophysiology, to emphasize the theoretical contributions and the scattered experiments, however inadequate they may be, which have started us over new and uncharted roads. The tracing of nerve impulses to the cortex, or from it to the effector systems, is not enough. We need to know how messages are coded,

filed, and recovered upon demand; how patterns of nerve impulses become percepts and images; and how they participate in thought, and eventuate in action.

New concepts of how neurones are organized, how they interact, how they perform under different conditions, whether indicated by behavior, electrical potentials which signalize underlying activity, or even by introspection, may be valuable in helping map the course for the future. That new concepts are needed is reflected in a recent publication by Lashley (31), entitled "In Search of the Engram." This interesting and penetrating analysis and review of his and other workers' investigations concludes with some challenging statements which will be repeated here in attenuated form:

(*a*) It seems certain that the theory of well-defined conditioned reflex paths from sense organs via association areas to the motor cortex is false.

(*b*) It is not possible to demonstrate the isolated localization of a memory trace anywhere within the nervous system.

(*c*) The so-called association areas are not storehouses for specific memories. They seem to be concerned with modes of organization and with general facilitation or maintenance of levels of vigilance.

(*d*) The trace of any activity is not an isolated connexion between sensory and motor elements. It is tied in with the whole complex of spatial and temporal axes of nervous activity which forms a constant substratum of behaviour. Each association is oriented with respect to space and time. Only by long practice under varying conditions does it become generalized or dissociated from these specific co-ordinates. The space and time co-ordinates in orientation can, I believe, only be maintained by some sort of polarization of activity and by rhythmic discharges which pervade the entire brain, influencing the organization of activity everywhere.

(*e*) The equivalence of different regions of the cortex for retention of memories points to multiple representation. Somehow, equivalent traces are established throughout the functional area. Analysis of the sensory and motor aspects of habits shows that they are reducible only to relations among components which have no constant position with respect to structural elements. This means, I believe, that within a functional area the cells throughout the area acquire the capacity to react in certain definite patterns, which may have any distribution within the area.

(*f*) Recall involves synergic action or some sort of resonance among a very large number of neurons. The learning process must consist of the attunement of the elements of a complex system in such a way that a particular combination or pattern of cells responds more readily than before the experience. The particular mechanism by which this is brought about remains unknown.

Lashley's concepts of patterning, the widespread representation of habits and memories, and the significance he attaches to timing and serial sequence are just a few of the features of his thinking which align with the models, theories, and speculations of Ashby, Eccles, Walter, Cragg & Temperley, Pitts & McCulloch, and others. This is not to say that he would agree with

each or any of these points of view, or for that matter that any of us would. Yet the results of years of research and clinical observation seem to be pointing in the direction of the need for new ways of envisaging nervous system function, ways which not only will encompass the facts of neurophysiology but will also square with the requirements of behavior.

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THE PHYSIOLOGY OF VISION[1,2]

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In his introductory article to the 1954 volume of the *Annual Review of Physiology*, Otto Loewi called attention to the gradual transference of interest, among students and research workers, from the function of the whole organ to that of its constituent cells and even to the organelles within the cells. Nowhere is this more noticeable than in the subject of vision where the exciting problems are those which relate the structural elements of the retina to the multitudinous functions which that outpost of the central nervous system performs. The problems are not only fascinating in their own right, but they also command attention because of the important information which their solution may yield about the neurones of similar origin elsewhere in the central nervous system.

In the same article Loewi also deplored the prevailing impersonality of scientific papers and the barren quality of much of the publication of accumulated data. Fortified by the opinions of so high an authority, I propose in this review to attempt some sort of correlation between certain biochemical, psychophysical, and electrophysiological aspects of vision on the one hand and the cytological and physicochemical properties of the retina and related structures on the other.

The problems selected, the methods employed, and the lines of thought followed by workers in these different fields are so diverse that mutual misunderstandings and misrepresentations are almost inevitable. I therefore make an immediate apology for any misuse of data which may find its way into this review. I do not claim to be expert in all those branches of the subject which must needs be considered and can only interpret the data as I understand them at the moment. I hope that such mistakes will not be numerous and ask to be forgiven by those authors who feel that their contributions to the subject have not been correctly interpreted or that they have not been given a fair hearing, or even have been given no hearing at all.

I feel more at liberty to adopt this course at the present time than I might upon other occasions, in view of the excellent summaries of recent work which have recently appeared by Chang in the *Annual Review of Physiology* (55a) and by Wald in the *Annual Review of Biochemistry* (215).

The present article will be arranged on the basis of the histological pattern of the retina, and I shall try to integrate some of the recent data on retinal function with the various structures with which they seem best to correlate. The article will in fact be almost exclusively concerned with this aspect of vision.

[1] The survey of literature pertaining to this review was completed in May, 1954.

[2] The following abbreviation has been used in this chapter: ERG (electroretinogram).

The Photoreceptors

In spite of the searching observations of numerous histologists from the days of Schultze and of Cajal to the present time, there is a tendency among many who work on vision, perhaps influenced by the excellent, if simplified, diagrams by Polyak to regard the rods and cones as if they were the black and white keys of a piano and to think of the neural mechanism behind them as being as rigidly determined as the piano wires. Reality is different. The retina is a cellular structure, and alive.

The rods.—In order to study biological material with the electron microscope it must first be completely dehydrated; and since such material often initially contains a very high percentage of water, it is somewhat surprising that the final product should bear much resemblance to the original structure. Nevertheless, electron microscope studies of the fragmented rods of the guinea-pig (189) and frogs (91), and of thin sections of rods (osmium-fixed) in guinea-pigs and perch (190, 191) reveal structures which, in spite of dehydration, seem to be closely related to those which have been deduced to be present by the use of polarised light on living, or at any rate surviving, rods (75, 76, 181, 182, 183). The laminated structure, which often shows itself in fixed preparations of the outer segments, is clearly revealed by the electron microscope and is shown to depend upon the presence of a series of double membranes. These flattened envelopes (about 14 mμ, in thickness) are probably protein in character, and it is likely that each contains orientated lipid molecules. They are comparable with similar structures in myelin sheaths and, interestingly enough, in chloroplasts (95).

Schmidt (183) and Denton (75, 76) have confirmed the dichroic character of the rods of the frog and salamander and have shown that the light-absorbing molecules, presumably visual purple, are orientated with their long axes at right angles to the long axis of the rod, i.e., they lie parallel to the protein lamellae but show no evidence of any regular arrangement in the other planes. After bleaching, they continue to be orientated in the same direction, but now the products absorb strongly in the violet and ultraviolet. In time, these products become disorientated and also cease to have much absorption in the visible spectrum. These changes are consistent with the view that indicator yellow has the chromophore group still bound to protein probably by a carbon to nitrogen bond (56, 59, 61), while the retinene (vitamin A aldehyde) is free from protein and may change to vitamin A itself (20, 215). Arden (5, 6), however, on grounds of spectral absorption, has raised doubts as to whether the yellow product of bleaching in the isolated rods of the frog is actually indicator yellow.

Histochemical methods, with the possible exception of the brown colouration produced by the Liebermann-Burkhardt reaction (100), have so far failed to reveal the exact location of the carotenoids or chromoproteins in the outer segments. Antimony trichloride in saturated solution causes a blue colouration in the oil globules in certain cones and in the pigment epithelium, but not in the outer segments of rods. The latter and the pigment epithelium

fluoresce in ultraviolet light (106, 170, 187, 188), but there are several possible causes for this see p. 344). Since Wald & Brown (217, 218) have shown that SH groups are liberated when rhodopsin is bleached, a histological investigation of the rods along these lines might prove fruitful. Lillie (142), by the use of the performic-Schiff reaction for ethylene bonds, detects large quantities of what he considers to be lecithin in the outer segments of rods after formalin or bichromate fixation.

Separation of the rods, by simple suspension in Ringer's solution, serum, or aqueous humour, or by flotation in sucrose (58, 133, 180), allows various detailed analyses to be made with less interference from other elements. Collins, Love & Morton (58) report that such rods contain 31.9 per cent (dry weight) phospholipin, 38.5 per cent protein, and a tantalising 22.6 per cent unclassified remainder.

Hubbard (124) has estimated the molecular weight of rhodopsin to be about 40,000 [c.f. Hecht & Pickels, 270,000 (119); Weale, 45,600 (225); Broda, Goodeve & Lythgoe, 26,500 per chromophore (48)] and has estimated the rhodopsin content of the outer segments of cattle rods to be about 4.2×10^6 molecules and that about $\frac{1}{3}$ of the protein of the outer segment is rhodopsin. The rods of the frog, being very much larger, contain about 500 times as much, but the concentration is only about 2.5 times that found in the cow. Denton & Pirenne (79) estimate on the basis of sensitivity measurements that in the human rod there must be about 7×10^7 chromophore groups. Several other estimates have been made of the visual purple content of the rods in various species by measuring the optical density of the whole retina or of isolated rods before and after bleaching, or by measuring the density of extracts and, rather dubiously, assuming an even distribution of the pigment in the retina. The results may be tabulated (see Table I).

Since in many retinae there is much space which is not occupied by rods, and since the extraction may involve loss of pigment, estimates from extracts can be regarded only as an approximation. Moreover, Denton & Pirenne (79) have pointed out that, because of the dichroic character of the rods, estimates from extracts may, for this reason also, yield lower values than the same amount of visual purple would actually have in the retina. A factor of about 1.5 may be involved.

In the above discussion it has been rather assumed that all rods are similar and all contain rhodopsin. The extensive studies by Wald (211, 213) and others and more recent studies by Dartnall (70) emphasise that this is not necessarily so. It is now clear, that, in addition to the definitely different visual pigments, rhodopsin and porphyropsin, extractable from rods, where the difference lies in the chromophore group of porphyropsin having an extra double bond in the ionone ring (89) and where the two pigments are derivatives of vitamin A_1 and vitamin A_2 respectively, there are also species variations in the spectral sensitivities of the two pigments which are probably dependent upon the protein fraction of the molecule. Human (64), bovine, and rat (61, 212) rhodopsin all have maxima in the region of $\lambda = 497$ to 498 mμ,

TABLE I

VISUAL PURPLE CONTENT OF RETINAE AND RODS

Species	Density (average)	Density (per rod)	Author
Frog	1.08		Segal (185)
	0.52	0.76	Denton (77); Denton & Wyllie (80)
	0.54		Broda, Goodeve & Lythgoe (48)
	0.25		Dartnall (70)
		0.50	Hubbard (124)
Bull-frog	0.178		Wald (210)
Rat	0.061		Wald (210)
Albino rat	0.6		Segal (185)
Rabbit	0.019		Wald (210)
Albino rabbit	0.2		Hagins & Rushton (110)
Cattle		0.037	Hubbard (124)
Man	0.016		Brindley & Willmer (47)
	0.016		Crescitelli & Dartnall (64)
	0.06		Campbell & Rushton (53)

while frog rhodopsin (70, 212) is most sensitive at about 502 mμ, and that of the squid (179, 212) at 490 mμ. Dartnall has described pigments with maxima at 510 mμ (68), 519 mμ (71), and 523 mμ (65); and the last, from the carp, is clearly distinct from typical porphyropsin whose maximum lies in the region of 533 mμ, though it may well contain retinene$_2$, since vitamin A_2 is found in the livers of freshwater fish which are fed on carotene (154). Incidentally, although the correlation is not absolute (60), vitamin A_1 and rhodopsin still seem to be associated with marine and terrestrial life, while vitamin A_2 and porphyropsin preponderate in animals living in a freshwater environment. In a recent paper on the vitamin content of livers of fish in the Nile (1) it is noteworthy that the only two fish containing vitamin A_1 in their livers are *Tilapia*, which is found in the delta, and the migratory *Anguilla*. Such findings are suggestive that the effects on vision (i.e., the presence of rhodopsin or porphyropsin) are purely secondary to some, as yet unappreciated but probably much more general, metabolic effect, as, for example, on the salt balance or water economy of the animals.

Even among the rods themselves, in any one species, there are sometimes more than one class, each containing a different pigment, thus complicating the interpretation of spectral sensitivity curves (78). The red and green rods of certain amphibia are well-known, and Denton (77) has, by an ingenious photographic method, shown that the green rods have a spectral absorption both in the blue and in the red, which is thus quite unlike that of the ordinary red rods and in general form more resembles the spectral sensitivity of certain chromoproteins based on astaxanthine (192). Differentiation into classes among rods has also been noted by Sjöstrand (191) in his study of the inner

segments of the rods of the guinea-pig. Furthermore, certain staining differences, probably indicating structural differences comparable with those described by Sjöstrand, are also to be observed among the inner segments of the rods of certain monkeys (139). In the guinea-pig, the difference is related to the number and distribution of the mitochondria. Sjöstrand (191) and Elfvin (88) have shown that the inner segment of the rods in the region of the ellipsoid has well-developed and orientated mitochondria, thus confirming the earlier work of Leplat (140) and Lewis (141) and the more recent observations of Francis (100). Since mitochondria, which are thus probably the primary constituent of the ellipsoids, contain the cyclophorase system of enzymes, cytochrome-oxidase and succinic dehydrogenase, and since, also, succinic dehydrogenase has been demonstrated in considerable amount in the ellipsoids of both rods and cones (98), it is clear that the inner segments of both rods and cones are very active metabolically. This activity may be concerned with pigment synthesis and breakdown, for Wald and his colleagues (212, 213, 216) have clearly demonstrated the role of dehydrogenase in retinene metabolism; or it might relate (191) to the still unsolved and fundamental problem of the transfer of activity from the photochemical response in the outer segment to the more centrally situated neural mechanisms. On this latter point Wald (212, 216) has put forward some interesting suggestions which incriminate the SH-groups, which he has shown to be liberated when rhodopsin is acted upon by light, and there are some very relevant and parallel observations on the eye of *Sepia* by Chalazonitis & Arvanitaki (54, 55). In a brief histochemical paper by Wislocki & Sidman (237), in which no details are given, it is stated, among other things, that the rod outer segments are rich in sulphydryl. This perhaps gives point to the hypothesis that 6.8 thioctic acid may be involved in vision as it is in photosynthesis (193).

Since the mitochondrial elements are so important, it is essential to know, in studies of the activities of "isolated rods", whether the "inner segments" which contain the mitochondria have remained attached to the "outer segments" or not. These last two terms should only be used to indicate the two parts of the rods or cones proper, i.e., those parts of the rod and cone cells which lie outside the external limiting membrane. Hubbard (123) has shown that the respiration of frog "outer limbs" is increased by fructose diphosphate and by succinate and is cyanide-sensitive, but the paper is vague on the exact meaning of outer limb, and it is not clear whether the ellipsoids are present or not. Moreover the experiments were performed in Ringer's solution, and Arden (5), who is equally vague on the subject of the presence or absence of ellipsoids, has pointed out that "outer segments" are preserved for much longer in sucrose than in Ringer's solution, though he offers no evidence as to whether or not they remain metabolically active. Ottoson & Svaetichin (163) also comment on the ill-effects caused by Ringer's solution on electrical recordings from the frog's retina; they recommend the use of aqueous humour or of isotonic glucose. Many years ago the far-reaching

effects of the medium upon the metabolism of the retina were firmly pointed out by Warburg and his colleagues (224). It seems important here, since several methods have now been described for isolating the visual elements or parts of them (5, 58, 133, 180), to emphasise the necessity that in all future work the exact details should be given, together with an analysis of the cytological and metabolic effects of the various procedures.

In the light of these strictures it is a little difficult to assess the physiological value to be attached to the findings of Collins, Green & Morton (57) on the requirements of such specific agents as adenosinetriphosphate, cytochrome-*c*, vitamin A, succinate, etc. for the regeneration of visual purple by ground-up mixtures of retinae, pigment epithelia, and choroid, suspended in what is essentially a phosphate buffer with the addition of all the reagents under investigation except one. Under the best of their conditions they claim that regeneration is complete within the hour, and somewhat naively compare their results with the normal process of dark-adaptation. Sugita (194) records a 20 per cent increase in oxygen up-take by frog's retina during dark-adaptation.

There is general agreement that flavin compounds are abundant in the eye, but their exact role and location is obscure. In the eyes of Swedish frogs riboflavin has been localised by its fluorescence (187) to the choroid. In Russian frogs, unless specially fed, it is absent but may appear in the rods, cones, and pigment layer. In rats (173) from the same country it is found in the rods, cones, and pigment layer and is more abundant in the retinae of dark-adapted animals, while in Japanese frogs (239) flavine compounds, estimated as lumiflavin, are most abundant in the choroid; in the retina itself there is an increase with light-adaptation, and flavine is present as mononucleotide. How far these conflicting views arise from inadequate methods of localisation, estimation, and analysis, and how far they are genuine differences remains to be seen. Nevertheless the effects of flavin compounds, cytochromes, and perhaps porphyrins (134) also, together with the nature of the reflecting surface behind the eye, which may or may not be developed into an actual tapetum, should not be neglected in considering the significance of any variations from the typically smooth spectral sensitivity curves of carotenoid chromoproteins (70). The quite large effects of the cat's tapetum have been described by Weale (226).

By direct observation and by photoelectric recording, the density of pigment absorbing in the region of 500 mμ in the living eye of the albino rabbit (110) and, more recently, in man (53) and also in the cat (229), and the effects of light- and dark-adaptation have been studied *in situ*, and it is fairly clear that dark-adaptation does not depend upon the concentration of visual purple alone. In the rabbit, visual purple was found in almost maximal concentrations even when the eye had been exposed to light some 100,000 times the human absolute threshold. Other factors in the problem of dark-adaptation will be discussed later. Meanwhile, by the same technique, Weale (229) has found evidence for a pigment in the cat's eye which regenerates much more quickly than visual purple.

Several Japanese workers have reported on the influence of various reagents upon the regeneration of visual purple. They confirm the earlier observations that acetylcholine and pilocarpine injections accelerate the process, but since they find that atropine, muscarine, and physostigmine have no action, that choline and betaine are more effective than pilocarpine (129), and that methionine exerts an augmentative action (128), they are inclined to the view that it is the lipotropic action which is chiefly involved.

The action of the melanophore hormone of the pituitary on the eye has been a controversial subject for a number of years (73, 111, 132), but the idea that the hormone might accelerate and increase dark-adaptation is interesting on account of the action of this substance on melanin-containing cells and chromatophores in general, for these are cells to which the retinal cells and pigment epithelium cells are phylogenetically rather closely allied. However, the new evidence (112) for its direct action on the chemical process of visual purple regeneration in the frog is not entirely convincing. There are many factors involved in measurements of visual purple regeneration, and it is not clear that the suggested explanation for the findings is the only possible explanation; for example, the preparation of the hormone used may well have contained one or more of the various catalysts, etc., which have been shown to influence the process (see above). Moreover, when the extreme sensitivity of the normal eye is considered, it is difficult to imagine a process which would, as Hanaoka (111) claims, lower the absolute threshold about one thousand times.

Perhaps one of the most interesting features in the structure of the rod which has been demonstrated by the electron microscope (191) is the fibre which joins the outer and inner segments. This probably penetrates for some distance into the outer segment and for a little way into the inner segment where it comes into intimate contact with mitochrondria and where it is continued as a cross-striated fibre. The part which connects the two segments consists of a bundle of from 16 to 18 fibrils arranged in two concentric rows, very reminiscent of the arrangement of fibrils in many cilia and flagella and in the tails of mammalian spermatozoa (43). So, too, does the cross-striated fibre of the inner segment compare with the rootlet fibres in ciliated cells (90).

In view of the probable embryological origin of rods and cones from flagellum-like processes (183a), and of the whole retina from that part of neuroepithelial tissue which in the frog embryo (14), for example, is early characterised by a ciliated band comparable with those of auricularia larvae of echinoderms or tornaria larvae of *Balanoglossus* (27), the concept of the outer segment of rods (and probably cones) as essentially modified flagella is of some interest, particularly when related to the part played by similar "hair-processes" in other sensory cells, e.g., hair cells of the cochlea and cristae, of the olfactory organ, of taste-buds, and lateral line organs. The connection between mitochondria, as basal granules, and cilia and flagella is well-established, and certainly in the retinal rods the connection between mitochondria and the place of origin of the outer segment has become very conspicuous.

The cones.—The widespread belief in highly sensitive rods as agents for scotopic vision and less sensitive cones for photopic vision is now coming to be considered as altogether too simple a concept, and, while it is true in general, it may well be incidental to the essential differences between rod and cone cells as two separate races which link up with different neural elements. This idea has been discussed in several papers by Willmer (230, 233, 234) and in the last few years has received further support from several different sources. In the first place, Sjostrand's electron microscope studies (190) of the rods and cones in the retina of the perch show a fundamental difference in the construction of the outer segments of the two cell types. While the outer segment of the rod consists of a series of double membranes enclosing lipid, that of the cone is composed of a pile of thicker (17 mμ) single membranes. Secondly, by the injection of sodium iodoacetate into rabbits, cats, and monkeys, Noell (160) has shown that the visual cells are selectively damaged, and that it is the rods which suffer first and most extensively. In the monkey, the rods are most damaged near the centre of the fundus and least so near the ora serrata, while the cones, which are in general less severely affected than the rods, are most damaged in the periphery, leaving the foveal cones comparatively unharmed. Thirdly, in retinitis pigmentosa and in a similar hereditary disease in certain breeds of dogs (165, 166) there is a very similar selective damage to the rods. In animals treated with iodoacetate (159), the electroretinogram (ERG) shows an immediate decrease in the *b*-wave (the wave which is often associated with rod activity) and a longer persistence of the negative *a*-wave which may be temporarily enhanced before it too is abolished. The *a*-wave has been associated more with cone activity (*see* below). In the abnormal dogs, however, though the *b*-wave was similarly abolished, there was no enhancement of the *a*-wave.

One of the burning questions concerning the cones is, of course, the nature of the pigment or pigments which they contain. As with the rods, there are probably variations from species to species, but the reports by Wald (215, 219, 220) on the formation *in vitro* of both iodopsin and cyanopsin are of considerable interest. Iodopsin (max. 562 mμ). the pigment extractable from the retinae of birds, has been formed *in vitro*, together with rhodopsin, from retinene$_1$ and protein extracts of chick retinae, so that it seems probable that the cones and the rods, in this species at least, both depend upon the same carotenoid. Moreover, just as rhodopsin in the rods can only be synthesised from a cis-isomer of retinene (125, 214), so is this also true of iodopsin, and likewise the bleaching of iodopsin yields only the inactive all-trans-retinene. When retinene$_2$ is used instead of retinine$_1$ in conjunction with the protein extracts of chick retinae, porphyropsin and the new pigment cyanopsin, with its maximum absorption at 620 mμ, are formed. This latter pigment is probably directly comparable with the one which activates the cones in such animals as *Testudo graeca*, and the freshwater fish *Tinca*, both of which are believed, though the former without direct proof, to possess vitamin A$_2$ in place of vitamin A$_1$. Electrophysiologically these two animals both show

high spectral sensitivity at 620 mμ (104). These important observations again emphasise the distinction between rods and cones; for the cell proteins in rods (scotopsins) give rise with retinenes to rhodopsin and porphyropsin, while cone proteins (photopsins) correspondingly yield iodopsin and cyanopsin. The surprising feature of this situation is the very large shift in spectral sensitivity which the protein fraction of the chromoprotein causes.

Up to this point it might be thought that recent work had clarified the problem of visual pigments, but there remain many complications. For example, Dartnall has produced evidence for visual pigment 467 (λ max. = 467) (67) in the retina of the tench (*Tinca*) and 510 (68) in the bleak (*Alburnus lucidus*); and now Wald, Brown & Smith (221) have reported a pigment, based on retinene$_1$ with max. between 525 to 530 mμ, in the marine scup and a pigment with λ max. at 550 mμ in two fresh-water fishes and a marine fish, and this pigment yields retinene$_2$. The site of these pigments in the living eye is not known.

All the pigments so far mentioned have this in common, that the shape of the spectral sensitivity curve when plotted against wave-frequency rather than against wave-length remains almost the same, but the maxima occur in different parts of the spectrum (70). There are now, however, indications on directly photochemical evidence, as distinct from less direct analysis of electrophysiological data (86, 105, 236) of the existence of pigments with much narrower bands, one at 535 mμ in the frog (7) and one, rather more doubtfully, at 565 mμ in *Xenopus laevis* (69).

One may perhaps tentatively conclude that the rods and cones, originating from somewhat different cells, have built up similar photochemical systems; but the two systems are not identical, probably because of the different properties of the basic cell proteins, and, in both types of cell, numerous variations on the original theme have occurred.

The ellipsoids of cones are again essentially mitochondrial in character and give the same reactions as those of rods (98, 141). In the primate retina there is a class of cones in which the "myoids" can be stained intensely after suitable fixation and which can thus be distinguished from the majority (139). These dark cones are most numerous in and around the fovea. While not universally present, a paraboloid, containing Schiff-positive material, is a feature often found in cones, and with one or two doubtful exceptions it is absent from rods. The exceptions include the geckoes and urodeles, and in the geckoes the so-called rods have properties, e.g., flicker fusion frequency (66), which are more characteristic of cones.

Electrophysiology of the receptors.—An eye which has been much studied from the electrophysiological angle is that of *Limulus*, on the assumption that in this animal impulses arise from the photoreceptors themselves and can be picked up before they are influenced by any neural connections. Some re-orientation of this viewpoint seems now to be necessary in consequence of a reinvestigation of the cytological structure of the ommatidia (117, 153). It now appears that each ommatidium is composed of several retinula cells

clustered round a central laminated structure, the rhabdom; and there is, in addition, a large eccentric cell. Both sorts of cell give off fibres centrally, and these join a plexus just below the ommatidium. Electric recording indicates that there is interplay between neighbouring parts of the eye, which is presumably mediated by this plexus (115, 117).

Before discussing the significance of this and other recent electrophysiological work, attention may first be called to the similarity between the laminated character of the rhabdom in these ommatidia of invertebrates and the laminated outer segments of both rods and cones in vertebrates. Since the two structures are of fundamentally different origin and produced in entirely different ways, their similarity is striking and may provide a clue to some essential step in the process of visual excitation.

Investigation of the electrical activity of the ommatidia of *Limulus* with very small electrodes (116, 117) has shown that when light shines on the eye, the distal end of the retinula becomes electronegative; a slow ommatidial potential develops. Probing of the retinula cells with micropipette electrodes generally yields little, but occasionally the micropipette becomes suddenly −50 mv., and this is thought to be caused by the penetration of the eccentric cell. The nerve bundle simultaneously discharges impulses. When light is then shone on the ommatidium, the micropipette becomes less negative, and impulses can again be recorded. Direct current passed across the eye (cornea cathodal) sets up nerve impulses immediately, with a very short latent period. Light of the appropriate intensity may set up the same number of impulses, but the latent period is longer, perhaps indicating the duration of the photochemical excitatory process. Electric current passed in the opposite direction (cornea anodal) produces on off-effect but has no action at "on." It is noteworthy in these experiments that the ommatidia show slow potential changes in response to light and that the impulses probably originate only from the eccentric cells. It will be remembered that slow potentials were the only effects recorded by Parry (164) from the retinula fibres in the ocellus of an insect, and electrical recording across the retinula layer only (i.e., without the ganglion cell layers) in the compound eye of a fly (*Calliphora*) yields only slow potentials (17, 18). Moreover, no one has yet succeeded in recording impulses from the actual receptors in any vertebrate eye, and it is becoming increasingly probable that the primary response to light is the development of a slow potential. Evidence is now accumulating which indicates that the elecroretinogram originates in and is primarily attributable to changes in the receptor layers, though Tomita and his school (201, 202) have made observations which lead them to think that the bipolar cells are the source of part of the b-wave and of *P*III. In the first place, the latent period of the ERG[2] (a-wave at least) is shorter than that for any impulses which have been recorded from the eye (3, 28, 30, 202). Secondly, though this is obviously not a conclusive argument, the ERG is reduced and may disappear when the receptor layers degenerate (see p. 346). Thirdly, and with the same reservations, rods develop embryologically before cones,

and the *b*-wave develops before the *a*-wave (74, 240). Finally, in some recent work by Ottoson & Svaetichin (163), who used extremely fine (0.5 μ) electrodes to penetrate and record from the different layers of the retina of the frog, there is strong indication that the crossing of the external limiting membrane by the electrode tip is a critical point in determining the size of the electric response obtained to flashes of light; when, with an indifferent electrode on the vitreous surface of the retina, the exploring electrode was pushed outwards towards the receptors, a sudden change in the potential recorded in response to light occurred at a depth of some 170 μ and alternatively, with the indifferent electrode on the free surface of the receptor layer, large potential changes were recorded only when the exploring electrode tip lay between 175 μ and the internal limiting membrane. Moreover, by changing the temperature they showed that the ERG would persist after the propagated disturbance in the optic nerve had failed. Similar results were obtained with urethane and cocaine, which incidentally also produced rather different effects on the shape of the ERG, the former, like alcohol (29), decreasing the *a*-wave and the off-response, the latter increasing them (162).

The authors have continued these studies (161, 162, 163) on the retina of the frog and by using extremely fine KCl-filled capillary electrodes (0.5–1 μ) they conclude that there is a steady potential of from 6 to 10 mv maintained along the length of the receptors, and this is sometimes increased and sometimes decreased in response to light. The potential falls when the eye is cooled or treated with NaF, NaCN, ether, etc. The authors conclude that the positive responses originate in rods, while the negative responses originate in cones. This is certainly in keeping with the numerous indications that the negative part of the ERG is particularly connected with cone activity (see, however, p. 350). For example, Dodt (84) and Dodt & Wirth (85) have studied the ERG produced by flickering light in different animals, and on the basis of fusion frequencies, have concluded that the *b*-wave relates to rods and the *a*-wave to cones, a conclusion also reached by Svaetichin (196). Similar observations have been made by Bornschein (31) and by Bornschein & Schubert (32).

By actually puncturing the inner segments of cones and the ellipsoids of rods with micropipette electrodes, Ottoson & Svaetichin (161) claim that there is in each case a membrane potential of some 70 mv, the inside of the cell being negative.

Pursuing these studies further, Svaetichin (195) has transferred his attention to the retinae of the bream and the perch where the cones, in particular, are considerably larger than in the frog and constitute a rather well-defined layer near the external limiting membrane. Very similar results were obtained. At the appropriate depth of the exploring electrode a sudden drop of about 70 mv occurred in the contact potential, and this means, he concludes, that the inner segment of a cone has been penetrated. As long as light falls on the cone the negative potential is increased contemporaneously by a steady amount which varies with the intensity of the light. The relationship

is such that the amplitude of the potential change varies with the logarithm of the stimulus intensity in a manner very comparable with that in which the frequency of impulses varies in the optic nerve of *Limulus:* over the middle range of intensities the amplitude varies linearly with log intensity. The latency of response is found to be almost constant and independent of the strength of the stimulus; the records also suggest that the total response is simply dependent upon the product of the intensity and the duration of the stimulus for flashes lasting between 0.4 and 400 msec.

In response to equal energy light stimuli of different wave-length, certain individual cones (35 out of 63 tested) gave different amplitudes of response at different wavelengths, and the author tentatively suggests that there may be four classes of cone with different spectral sensitivities. It is, however, not clear how the stimuli were applied, how intense they were, what state the retina was in, what contamination there was likely to be from blood, other pigments, or scattered light, or what steps were taken to ensure that there was no chromatic difference of focus in any lens system employed. Consequently these results cannot yet be taken at their face value.

This approach to retinal physiology, by probing individual cells, is so fundamental and important that one may perhaps be allowed to express disappointment that the authors have not given more detailed accounts of their experiments. Observations on the eye are so often capable of several interpretations that it is vitally important, if others are to be able to assess the results, for the exact conditions of the experiments to be stated. In the papers which have just been discussed there are too many points at which the reader is unable to evaluate the results because of lack of information, and it is to be hoped that the work will be followed up in the near future in greater detail.

It was mentioned above that the initial negative phase of the electroretinogram seemed to be particularly associated with cone activity. This is, in fact, probably an oversimplification and only partly correct. The electroretinogram of those animals which have numerous cones shows evidence for the existence of a fast as well as of a delayed component, and the former is most purely obtained under photopic conditions with red light (2, 10, 11, 12). Both components probably have an early negative phase followed by a later positive phase, but the quicker component has a second negative phase. With red light a distinct positive X-wave appears on the normal human ERG, and it is significant that not only is it absent in cases of total colour-blindness (209), but it is much reduced in the ERG records from protanopes (10), who, among all the various types of colour-blind subjects seem perhaps to be the most likely to have an actual absence of one class of receptors. The size of the X-wave has a high rate of recovery after previous stimulation and thus resembles the dark-adaptation of cones. It may well be a measure of the activity of the so-called "red" cone. The effects are most obvious at about $\lambda = 630$ mμ, but because of the complexity of the records it would be

unwise to conclude that this type of cone necessarily has maximum sensitivity at that wavelength. The ERG of the squirrel, which has an all-cone retina, shows something like the X-wave (198).

By an ingenious method of substituting one colour for another in stimulating the eyes of turtles and frogs, Forbes & Burleigh (50, 97) have found that every change was accompanied by a detectable change in the ERG. Although some of the effects resulted from changing from rod to cone activity or vice versa, the authors concluded that several types of cone were probably involved.

Psychophysics and the photoreceptors.—Although less objective as measures of cone activity than some of those already discussed, certain observations on the visual thresholds of colour-blind subjects could be interpreted as evidence for the spectral sensitivity of cones. The spectral sensitivity of three cone-monochromats is discussed by Weale (228). Apart from differences in the blue part of the spectrum, which may relate to pigmentation, the mean curve is very similar to the central foveal sensitivity curve for protanopes, who are themselves monochromatic under these restricted conditions (231). The λmax. was found at about 540 mμ. Because field-size alters their spectral sensitivity, and because these observers were found to behave as though they had the chromatic stimulus to the accommodation reflex, as distinct from the achromatic (93, 94), it cannot be regarded as certain that they possess but one type of cone receptor. Abnormalities of colour vision may occur more centrally than the retina. Similar strictures on other grounds hold also for the monochromatic central fovea of protanopes, and it is of interest that Jaeger & Kroker (130) have shown that protanopes and deuteranopes are each divisible into two classes according to whether they still have a neutral point in the spectrum with large field sizes. Incidentally the observations of Fincham (92) and more recently of Campbell (52) make it quite clear that the accommodation reflex is initiated by the foveal cones, and both authors consider it likely that the retinal-direction effect may be involved.

Brindley (45), by adapting the eye to extremely bright lights, has produced states of artificial monochromatism. After adaptation to violet and then to red the resulting spectral sensitivity curve is very similar to that of the protanope and of the monochromats described by Weale (228). After adaptation to violet and blue-green the sensitivity curve resembles that for the cental fovea of some deuteranopes (232). Adaptation to violet alone produces tritanopia, comparable both with foveal tritanopia and also with the more general from which has now been more thoroughly investigated and recorded by Wright (238). By adaptation to intense yellow light, Brindley produced a state of violet monochromacy. All wave-lengths from 400 to 500 mμ could be matched with 447 mμ and, unlike the other monochromacies which are characterised by unsaturated hues, all these wave-lengths appeared intensely violet. In this violet range, intensity discrimination and

acuity were both much worse than in the other states of monochromatism. This observation and others (46) suggest the convergence of many blue receptors on to a single ganglion cell.

Another important finding in this work (45) is that the upset in colour matches which occurs after adaptation to high brightnesses is systematic and that the nature and extent of the upset is consistent with the view that only the red receptor is involved. It is suggested that this receptor initially has a high density of pigment (0.5) which is decreased by adaptation; it is also suggested that since the Stiles-Crawford effect is much reduced after adaptation to bright lights the high density of pigment may contribute to the effect.

Some other investigations on visual thresholds and spectral sensitivity, although certainly involving bipolar cells and ganglion cells, may now be considered because they relate primarily to the activity of the receptors. Weale (227) has systematically studied the photopic spectral sensitivity of the peripheral retina with 50′ fields located at intervals up to 70° off the fixation area. His results make it quite clear that, in the periphery, there is a rise in the sensitivity to blue light which is much greater than that which could be accounted for by the absence of macular pigment; though whether he is justified in drawing conclusions concerning receptor sensitivity from the other irregularities on the curves obtained is more questionable. The retina obviously behaves differently in its different regions and at different states of adaptation, and Weale appositely insists that variations in the neural mechanism must be involved and should be investigated. It is of particular interest to find that the periphery of the human retina has a very similar spectral sensitivity, both scotopic and photopic, to that of the cat's retina as a whole (108, 109). Histologically the periphery of the human retina has much in common with the cat's retina.

Working within the strictly physiological range, as opposed to the high brightnesses used by Brindley, Jameson & Hurvich (127, 131) have examined the effects on the foveal sensitivity curve, both at threshold and at several brightness levels, of adaptation to "perceptually unique hues." The curves are certainly modified, but because of the uncertainty in the physiological meaning of "perceptually unique" the physiological interpretation is not easy.

In the matter of macular pigmentation, direct measurements and comparison of the reflection of light from the central area and from a peripheral area of the human fundus have revealed the presence of a screening pigment over the normal living human foveal region whose absorption in the blue and blue-green parts of the spectrum is consistent with earlier estimates made by more ambiguous, if more exact, methods (47). Studies on the Haidinger effect (158, 208) point to the origin of the effect as being in a prereceptoral distribution of xanthophyll, and the distribution corresponds roughly to that of Maxwell's spot. Work along similar lines with colour-blind subjects may perhaps clear up the questions raised by Walls & Mathews (223) on the relationship

between the entoptic appearance of the spot and macular pigment on the one hand or receptor distribution on the other.

Ségal's suggestion (184) that the macular pigment is located in the inner (Henle's) fibres of the cones, though based on a somewhat dubious foundation, except in so far as a similar suggestion was first made by Helmholtz (121), certainly accounts for several peculiarities of the fovea, including the effects seen with polarised light, since these fibres are orientated radially from the foveal centre, and also the peculiar pattern of Maxwell's spot, which would depend upon the total thickness of absorbing pigment. The particular pattern of both effects would be determined by the number and direction of the fibres in the path of the light. It does not, however, so readily explain why Maxwell's spot is not seen by deuteranopes (223) and it would be interesting to know if such subjects see Haidinger's brushes.

The Bipolar Cells and the Synaptic Layers

By comparison with the receptors and with the ganglion cells the intervening cells are still very much an uncharted zone. Attempts to detect chemical transmitters in the synaptic layers (4, 99, 118, 135) have associated acetylcholine with the synapses between the bipolar cells and the ganglion cells by detecting cholinesterase, but elsewhere they have failed to show anything very convincing. There is much lipoid material in the synaptic layers, and this gives reactions for cholesterol (100). Esterases have been detected histochemically by a method based on the formation of indigo (26) in rods and cones and in the synaptic layers (237). In studying the glycogen content of eyes Shimizu & Maeda (186) claim that the Muller fibres contain more in dark-adapted than in light-adapted guinea-pigs.

Ottoson & Svaetichin (162), using their very small electrodes, claim to have picked up impulses from cells in the bipolar layer where Tomita & Funaishi (200), using larger electrodes, had previously failed.

Apart from these few observations and some points which may be deduced from retinal behaviour as a whole and from ganglion cell behaviour in particular, the last few years have contributed little direct information on the physiology of the intermediate layers. Some earlier papers by Vilter (205, 206, 207), however, called attention to the eyes of certain fish in which the rods and cones are concentrated in different halves of the eye, and they note, as Tansley & Arden do in the squirrel eye (198), the close correlation between the number of cones and the number of bipolar cells. This once again emphasises that one of the principal differences between rods and cones lies in the character of their central connections.

Ganglion Cells and Nerve Fibres

Ever since Rushton (176, 178) demonstrated that the majority of records of nerve impulses from the retina had in the past probably been taken from large ganglion cells only, there has been a tendency to enquire more

deeply into the spatial characteristics of stimulus and response and into the dimensions and properties of the receptive fields of the ganglion cells (23, 24, 137, 138). It has been shown that the retinal nerve fibres give rise to a rapid triphasic potential while the ganglion cells yield a slower diphasic change, generally of greater amplitude, so that it is now possible to locate the electrode more precisely on one structure or the other (23, 103, 137, 138). The problem of exact location has been approached partly by the use of more refined optical equipment (197) which delivers smaller stimuli with greater accuracy, and partly by the use of the unopened eye both in the cat (137, 138), in rabbits (199), and monkeys (199a). Moreover, impulses have been successfully recorded (199) from the optic nerve intracranially, without gross interference with the eye or its blood supply.

By the use of these accurately localised stimuli, the earlier work of Hartline (113, 114) on the receptive fields of ganglion cells has been amply confirmed and extended; but perhaps the most striking point about these newer records from the cells is the great variation in the character of the response with the stimulus strength, the size of the exploring spot, the state of adaptation of the eye (23, 24, 87, 137, 138, 199), and probably also from species to species. Kuffler (138) describes receptive fields of ganglion cells of the order of 1 mm. in diameter, and for a given size of stimulus the geographical centre of the field generally has the lowest threshold. The threshold response from the centre may, however, be either at "on" (on-centre unit) or at "off" (off-centre unit). Light falling in the vicinity, or simply enlargement of the stimulus area, may alter not only the size but also the character of the response. The peripheral part of the receptive field under these conditions generally opposes the activity of the centre; e.g., on-centre units can give an "on-off" or "off" discharge, and off-centre units can be inhibited by stimuli falling some distance away. As their histology indicates, ganglion cells collect information from wide areas, and, furthermore, both Kuffler (138) and Barlow (24) have shown that light falling outside the true receptive area, i.e., outside the area in which a light will evoke impulses from the ganglion cell, may nevertheless modify the discharge of the ganglion cell. In their most recent work Barlow, FitzHugh & Kuffler (25) showed that in full dark-adaptation the receptive field becomes very large and uniformly summating throughout, i.e., the periphery of the field now summates with the centre, so that the antagonism between centre and periphery seems to be characteristic of moderately high illumination.

The latent period (138) may be reduced by increased intensity of the stimulus, by increase in the stimulated area, by dark-adaptation, and by centering of the stimulating spot.

In a fascinating discussion to his paper on receptive fields in the frog (24), Barlow relates his findings to the information which is flowing to the brain of the frog when light stimuli of different sizes, intensities, or hues are moving over the retina. He points out, among other things, the peculiarities of both "on-off" and of "off-units" in detecting movement and its direction. He also suggests that "on-off units", if comprising two types of receptor with differ-

ent spectral sensitivities, would detect movement in objects differing only in colour from their surroundings, thus providing the animal with additional information and a simple type of colour discrimination, which would probably escape detection by the usual methods for investigating colour vision. Even in man the importance of eye movements in the appreciation of colour is well recognised. These observations, stressing how the eye is used by the animal, make a most refreshing and valuable corrective to the more static ideas of retinal activity which are so often held. A similar comment might also be made concerning his paper on the visual acuity in the compound eyes of insects (21), which incidentally confirms the earlier observations of Mallock (151), though it is unfortunate that his analysis could not include the minimum angle for the detection of movement, for this has now (51) been experimentally determined as about one-third of the angle between adjacent ommatidia, by recording the impulses from the circumoesophageal nerves of a locust.

Kuffler (138) also considers how the brain decides which are "on-effects" and which "off-effects." In connection with such difficulties and with the need for some standards, Barlow, FitzHugh & Kuffler (25) find that in the decerebrate cat, the better the preparation and the less the anaesthesia the more activity is recorded from the ganglion cells in the absence of any specific stimulus, so that "information" has to be distinguished from "noise". Under these better conditions the absolute threshold, i.e., change of rhythm in response to light, is more nearly comparable with that found for the animal as a whole (107), thus partly answering the queries raised by Pirenne (168) as to why electrophysiology usually gave much higher threshold values than those found by direct visual observation. It would now appear that not all impulses result from the direct action of light. However, the idea of much background "noise" somewhat conflicts with the arguments of Denton & Pirenne (79, 167, 169), who conclude on the basis of certain reasonable assumptions that in man the average noise value is probably not greater than 0.5 against a mean "signal" strength of 7 quanta, and if the latter is really 2 quanta (39), then the noise must be even less.

The observations described above also show that anesthetics, particularly urethane, must have considerable damping effects on retinal activity; this is also borne out by the effects of urethane on the ERG (156, 157).

These electrophysiological studies, together with analyses of the process of dark-adaptation (33, 35, 38, 49, 152), determinations of absolute thresholds, in relation to duration (36, 37, 44, 72), area (8, 34, 41, 175) and position of the stimulus, estimations of the amounts of visual purple normally present in the retina (53, 177), and the amount of it bleached by lights of known intensity, have all progressively pointed more and more to the conclusion adumbrated many years ago by Lythgoe (150) and by Craik & Vernon (62), that purely photochemical reactions play a comparatively minor role in the process of dark-adaptation. Variations in the neural organisation of the retina from time to time seem now to be the more important events in allowing the eye its enormous range of effective sensitivity. Probably most of

the changes in the organisation of the receptive fields, as shown by the recordings from ganglion cells, result from changes in synaptic resistance (whatever that may mean) and from varying amounts of summation and inhibition. However, in view of the results of time-lapse cinematography of nerve cells and neuroglia (126, 149), in which the finer cell processes are seen to be in constant active movement, it is worth remembering that the retina develops phylogenetically and embryologically from a layer of cells in which (in various animals though not in man) photomechanical changes have been observed in at least four of the cell types (rods, cones, pigment cells, and iris muscles), and that therefore actual mechanical movement of synaptic terminals in man is by no means such an unlikely event as was supposed by Sherrington.

It has been suggested (167, 169) that the rods may be connected to ganglion cells in two ways; as large units for maximal sensitivity and also as smaller units which, though having a higher threshold, would increase the acuity of vision. Although there is some suggestion from studies on a complete colour-blind (120) that an eye apparently activated by rods only may have two different types of "unit" with substantially different thresholds, the changes in character of the receptive fields at different intensities should not be overlooked. Attention at this point may also be drawn to the fact that the "mop" bipolar cells form connections with the cell bodies of ganglion cells, while most other types effect connection with the dendrites. It is a sad reflection on our knowledge of the detailed neuroanatomy of the retina that almost any suggestion with regard to the connections between the rods and cones and the ganglion cells could be postulated without much fear of definite contradiction.

Although on the surface it appears that the ganglion cells and bipolar cells are undamaged by the doses of iodoacetate (160) which selectively destroy first the rods and then the cones, there is in these experiments perhaps a chance to find out more about these cells by following the later history of such selectively damaged retinae. It would be valuable to know if any bipolar or ganglion cells eventually show changes in consequence of the loss of the receptors.

Some measurements of the subjective brightness of small fields of different wavelength in the human fovea (235) indicate that in this area also the receptive fields become smaller in light-adaptation than they are in the fully dark-adapted state. Similarly Bouman (34) has shown that the summation area varies with the wavelength but that the summation time is independent of it. Brindley (46), too, has just published a paper in which he concludes that the blue receptors have a much larger summation area than the red and green ones.

Some General Features of Retinal Physiology

We may perhaps summarise the present position by the following tentative conclusions. Light, however distributed within a critical time summates,

and the critical time is independent of wavelength. This is presumably a photochemical event, and retinal organisation does not enter into the picture. When numerous receptors are involved, then more or less summation occurs within certain definite areas. These areas are different for rods and cones and probably for different types of cones. They certainly vary with the state of adaptation of the eye, with wavelength, and with the activity of neighouring retinal areas. In these events the neural organisation is certainly involved, as it presumably must also be in order to account for the observation (155) that the effect of prolonged exposure to a low intensity of light has a greater delaying action on dark-adaptation than exposure to the same quantity of light delivered at high intensity.

A particularly interesting observation in connection with retinal interaction was that of Crawford (63), who showed that the threshold for a test field can be raised by the presence of an adapting field which is not illuminated till about 0.1 sec. after the test field has been presented. A similar finding is reported by Baker (19) in an investigation of the early phases of dark-adaptation. In this case the extinguishing of the adapting field is apparently preceded by a rise in threshold.

Crawford explained the effect in terms of suppression in the neural mechanism of the lesser stimulus of the test field by the greater stimulus of the whole adapting field. This is no doubt an explanation on the right lines, for, as Asher (13) recently and others before him have shown, the neural mechanism does normally suppress much of the information provided by the retina. Nevertheless, it is more difficult to explain the observations of Boynton & Triedman (42), who find that the *b*-wave of the electroretinogram suffers a similar though probably shorter prestimulation inhibition. This difficulty is especially great if we are correct in believing that the ERG arises in the receptors.

In view of the accent now placed upon neural integration in the retina, it becomes increasingly difficult to evaluate the events in ganglion cells in terms of those in the receptors. However, where cones are concerned it may be legitimate to assume that there is less pooling of information and more direct correspondence between receptor and ganglion cell. It is probably relevant to this problem that Arden & Weale (9) have found as the result of renewed interest in the meaning of the Pulfrich effect (83, 96, 174, 203, 204) that the latent period for vision at the fovea is much shorter than that for the periphery, and in the periphery there is a great increase in latency with decrease in light intensity, i.e., as summation becomes more important.

Such considerations probably increase the significance to be attached to the paper by Donner (86) on the recordings from the ganglion cells of the pigeon. He finds that the ganglion cells fall into three classes according to their spectral sensitivity, and he shows that such a result could be predicted from the modulator curves found by Granit (105) in the frog if the cones each possessed a filter, i.e., the oil globule, containing pigments similar to those which have been extracted from the chick retina (222). On this latter

point he would appear to be on dangerous ground because of the uncertainty as to the meaning to be attached to the term "modulator". Modulator curves may well result from summation and inhibition and hence have only indirect relationship to the spectral sensitivities of actual pigments. On the other hand it would seem likely, though admittedly it is not yet known, that the pigeon's retina contains iodopsin; yet the existence of this pigment has been quietly ignored, though it would not be impossible to derive the observed ganglion cell sensitivites by the action of filters on receptors dependent upon iodopsin-activated receptors.

It must have become abundantly clear from this survey and from the general trend of recent work on the eye that those text-books on physiology which state that cones, each with their own separate nerve fibres, are for day vision, while rods, which summate their effects on to ganglion cells, and are for night vision, make an altogether too naive simplification. It would seem likely that by a complicated system of playing one lot of receptors against another and by switching from one series of connections to another the eye integrates the information which it receives and passes it on to the brain over the minimum number of nerve fibres.

Much recent work by different methods on the movement of the eyes during fixation and during reading, etc. (15, 16, 22, 82, 122, 143 to 148, 171), makes it quite clear, among other things, that, except by the use of exposure times of less than 0.01 sec., it is virtually impossible to stimulate a single cone exclusively, even if the optical pathway were perfect, which it is not. There is general agreement that the eyes are always making small oscillations of the order of at least from 10 to 20″ with a frequency of about 50 c.p.s., but varying with different subjects, and, in addition, there are periodical flicking movements. Moreover, two groups of observers (81, 172) have independently examined in an objective manner the effects of stabilising an image on one position on the retina and have both concluded that under these conditions the image soon ceases to act as an effective stimulus and the object ceases to be visible, exept in occasional flashes, probably resulting from slight alterations in position. We may conclude, therefore, that eye-movements play an important part in normal vision. Measurements of acuity with stimuli of different duration (172) indicate that when the stimulus is so short that no movement is possible, then acuity is relatively high; with increased duration it falls off, probably because movement blurs the image more than the eye can compensate for by the increased information provided by the extra receptors stimulated; on further increasing the duration, the highest acuity is attained. Under these last conditions it is reasonable to suppose that the eye is synthesising the pattern of the image which is moving over the retina by integration, both in time and space, of all the "on" and "off" effects which modify the "resting" pattern. Even in the flash which allows no movement, the eye presumably transmits "on" and "off" effects to the brain. These results on form perception with "fixed" images are so interesting that an attack on the properties of the colour mechanisms along the same lines might prove

very valuable. For example, Brindley's experiments (46) on the "blue" mechanisms have indicated that the summation area is much greater than that for the "red" or "green" mechanisms. What is the effect of movement on the perception of blue? We know that small fields, especially when centrally fixated, though probably when immobilised elsewhere also, do not allow a full appreciation of their blue content.

Measurements of thresholds with very small fields has clearly shown that, when spatial summation is prevented, then the rods have much the same absolute sensitivity (8) as the cones, so that dark-adaptation when studied with fields larger than about 1′ and with flashes lasting more than 0.01 sec., must almost inevitably involve some degree of summation or neural interaction. Below these limits, the process of dark-adaptation is probably more purely photochemical, though it is likely that, even then, scattered light, which though small in amount has been shown to be quite significant (40, 47, 101, 102), will almost certainly vitiate the results, because with such short flashes the intensity of the light would have to be great and a significant amount would spread to neighbouring receptors.

Experiments with gratings of different sizes, as test objects in dark-adaptation, show that the smaller gratings are only resolved by cones while the larger ones are resolved by rods, so that the dark-adaptation curve shows the characteristic knee. In these and other experiments (49, 152) form perception always requires more light than the light threshold. These experiments perhaps show little more than did those of König (136), which established that acuity rises with illumination and that the rods and cones behave rather differently. What we do not yet know, however, is whether when we say "rods" and "cones" in the above argument we really mean rods and cones and not ganglion cells integrating from large and from small areas respectively, or perhaps ganglion cells acting under conditions of maximum summation as opposed to ganglion cells acting under conditions of maximum inhibition. Brindley's latest observations (46) on acuity certainly point in this direction. Then what about the bipolar cells, the horizontal cells and the amacrine cells?

The problems of the retina are not yet solved.

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THE PITUITARY AND ADRENALS[1,2]

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THE ADRENAL CORTEX

Aldosterone: A new mineralocorticoid from the adrenal cortex.—Probably the most significant addition to knowledge of the chemistry and physiology of the cortex during the past year has been the isolation and determination of the structure of aldosterone. It has long been recognized that after removal of all of the known crystalline compounds from cortical extract concentrates, there still remained in the mother liquor an active, noncrystalline residue designated simply as the amorphous fraction. Interest in determining the nature of this material was revived and greatly stimulated by the experiments of Tait *et al.* (1), Grundy *et al.* (2) and Simpson & Tait (3). These workers demonstrated the presence of a powerful sodium-retaining substance in adrenal vein blood; similar material was also found by them in extracts of beef adrenals which assayed twenty-five times the activity of DCA.[2] More recently Luetscher & Johnson (4) obtained from the urine of children with nephrosis an active sodium-retaining substance, presumed to be of adrenal origin, which resembled that reported by Grundy *et al.* (2). Farrell & Richards (5) isolated a sodium-retaining mineralocorticoid from adrenal vein blood of dogs, which upon assay proved to be twenty-five times more potent than DCA. Further studies on this material have been reported (6, 7).

Simpson *et al.* (8) were the first to isolate a pure crystalline compound which exerted an effect upon sodium retention greater than that displayed by DCA. The compound was provisionally designated as electrocortin and was said to be from 30 to 100 times more active than DCA, depending upon the test and animal employed. In separate publications which appeared only a few weeks later than that of the British and Swiss investigators, two groups of workers in this country (9, 10, 11) announced the results of their studies on the sodium-retaining factor extracted from beef and hog glands. Mattox *et al.* (10) obtained crystals which possessed mineralocorticoid activity equal to twenty-five times that shown by DCA. The material of Knauff *et al.* (11), although only about 20 per cent pure, when assayed using

[1] The survey of literature pertaining to this review was concluded June 1, 1954. Because of the large number of papers which have appeared during the year and the limited space allotted for review, only the anterior pituitary and adrenal cortex will be considered.

[2] The following abbreviations have been employed: DCA (desoxycorticosterone acetate); DOC (desoxycorticosterone); ACTH (adrenocorticotrophin); DDD [2, 2-bis (parachlorophenyl)-1, 1-dichloroethene].

the rat-growth test, proved to be equal to DCA in potency and was twenty-five times more active than this steroid in sodium-retention tests.

The chemical constitution of the new adrenal steroid was established by Simpson *et al.* (12) as 11β, 21-dihydroxy-3,20-diketo-4-pregnen-18-al, which reacts mainly as the 11-hemiacetal when in solution. They suggested aldosterone as a definitive name for the compound. Because of scarcity of material, few detailed physiological studies of the pure substance have appeared.

The potency of aldosterone when compared with that exhibited by DCA varies somewhat with the mammalian species and test employed but is approximately twenty-five times more active (10, 13). However, Speirs *et al.* (14) using rats, and the test devised by Simpson & Tait, found aldosterone to have 120 times the potency of desoxycorticosterone. Gross (15) and Gross & Gysel (16) report the steroid to be twenty-five to thirty times as active on adrenalectomized dogs as DCA when the latter is administered in oily solution. Swingle *et al.* (17, 18, 19) found the average maintenance dose of aldosterone to vary from 6.2 to 12.5 μg./dog/day when given in weak aqueous-alcohol to adrenalectomized dogs. It was from 12 to 25 times more active for maintenance than solubilized DOC,[2] and from 30 to 50 times more potent than DCA when the latter was given in oil. The minimum maintenance dose of solubilized cortisone and hydrocortisone for dogs lacking adrenals was 5000 μg./dog/day, which is 500 times more than the requirement for aldosterone.

This steroid differs physiologically in certain respects from DCA: (*a*) It is far more potent in retaining sodium; (*b*) according to Desaulles *et al.* (13) and Swingle *et al.* (17, 18, 19), it is less active than DCA in stimulating potassium excretion; (*c*) it has been reported (20) that aldosterone is thirty times more active than DOC in increasing the liver glycogen of mice. Gaunt (21) states that it shows potency as great as or even greater than cortisone when used on rats in the cold stress test but appears to lack the activity of the C_{11}-oxysteroids in the eosinophil depletion test. The reviewers are familiar with but one clinical trial of aldosterone (22). It was highly effective in rendering two Addisonians symptom-free, and the required dose varied between 150 to 200 μg. (2.5 to 3.3 μg./kg.) per day. The clinical symptoms were said to have disappeared a few hours after treatment began.

Adrenocortical activity of 9γ-halo derivatives of cortisone and hydrocortisone.—This series of compounds in which the 9γ-hydrogen atom is replaced by halogen was prepared by Fried & Sabo (23, 24). They are highly potent and have the distinct advantage over the parent steroids of possessing both mineralo- and glucocorticoid activity. Physiological studies show that their potency is inversely proportional to the size of the halogen atom.

Borman & Singer (25) examined the series for activity using rats and employing the following techniques: (*a*) liver glycogen deposition; (*b*) thymus involution; (*c*) ability to handle a water load; (*d*) survival time of immature adrenalectomized animals after a single injection of an aqueous suspen-

sion of steroids. The chloro derivative of both cortisone and hydrocortisone displayed surprising glucorticoid activity. In the hydrocortisone series, using cortisone acetate as a standard equal to 1, the activities of the fluoro, chloro, bromo, and iodo derivatives were 11, 5, 0.25, and 0.10 respectively. The ability of the adrenalectomized rats to handle a water load was considerably enhanced, and the 9γ-fluoro hydrocortisone acetate appeared to be ten times as effective as cortisone acetate in causing this response. Using the growth-survival and sodium-retaining tests, Borman, Singer & Numerof (26) found the chloro derivatives from ten to twenty times as active as DCA.

Leathem (27), made a comparative assay of chloro-hydrocortisone acetate and cortisone and found the 9γ-halo derivative to be more than 10 times as active in maintaining life than was cortisone. According to his data, chloro-hydrocortisone acetate has the same order of activity as DCA in the rat survival test but was superior to this steroid in permitting body weight gain.

Swingle *et al.* (28) assayed the chloro-hydrocortisone acetate in aqueous-alcohol solution, using adrenalectomized dogs, and found the minimum maintenance dose required to hold the arterial pressure, body weight, and serum electrolyte levels normal to be 55 μg./dog/day. However, the daily requirement for cortisone and hydrocortisone was 5000 μg. and for DOC, from 125 to 250 μg./dog/day. It is obvious that the 9γ-halo compounds deserve further study and clinical trial.

Cortical hormones and electrolyte distribution.—Some investigators hold the view that the sole effect of the adrenal cortex upon electrolyte metabolism is through its action on the kidney. Others believe that cortical hormones not only exert a renal action but also markedly influence the distribution of electrolytes between extracellular and intracellular compartments. To date, analysis of the soft tissues of animals in adrenal insufficiency has failed to give a conclusive answer to this problem.

Woodbury (29) investigated the extrarenal effects of adrenal hormones on plasma and tissue electrolytes in fed, fasted, and nephrectomized-adrenalectomized rats and concluded that these hormones influence electrolyte metabolism in all tissues of the body and, furthermore, that this influence is quite independent of the known effects of cortical hormones on renal function. Hills *et al.* (30) report that renal loss of water is not a prominent or a constant feature of acute adrenal insufficiency in man and that internal shifts of water, sodium, and chloride regularly occur and are prominent features of the disability. Other workers (31) have reported findings indicating that adrenal insufficiency in rats induces a gain of skeletal muscle potassium and a loss of muscle sodium. The animals lose more sodium from skeletal muscles than can be accounted for by changes in the volume and composition of the extracellular fluid space. Gamble (32), studying the effect of variations of sodium intake and of desoxycorticosterone on the relationship of sodium space to chloride space in dogs, states that his findings

indicate that adrenal cortical hormones can induce significant changes in intracellular sodium.

Flame photometry analyses of homogenates of muscle and brain and the ultrafiltrates of the homogenates revealed no noteworthy deviations between samples from normal and adrenalectomized rats. It was observed, however, that K^{42} counts did show a significant increase in specific activity (30 per cent) in samples from animals lacking adrenals (33).

Not all investigators agree with the view that during adrenal insufficiency or following administration of cortical hormones there occurs an internal redistribution of sodium along with a renal loss of this cation. Netravisesh & White (34) report that balance studies show that the quantity of sodium lost by adrenalectomized dogs during insufficiency closely approximates the amount retained during recovery. White & Rolf (35) in a further study of tissue electrolytes in normal and adrenalectomized rats offer data opposing the view that during insufficiency sodium moves into some sequestered site, e.g., bone. Grollman (36) observed that injection of from 50 to 100 mg. of cortisone daily into nephrectomized dogs increased the serum calcium to toxic levels. The calcium declined to normal serum levels upon cessation of the injections.

Carbohydrate metabolism.—A transient diabetes is produced in rats by long-continued cortisone injections (37). This steroid-induced diabetes may result from reduced glucose utilization because of inhibition of insulin activity by cortisone. Severe steroid diabetes in guinea pigs (38) produces great hypertrophy of the islets of Langerhans, increased body weight, obesity, glycosuria, and hyperglycemia; when cortisone treatment is stopped the diabetes slowly disappears. According to Ingle *et al.* (39) liver glycogen may attain very high levels in both fed and fasted rats exhibiting steroid diabetes induced by cortisone. This steroid increases the liver glycogen of fasted normal rats given glycine (40), but cortisone injections given daily to rats for several weeks do not have a cumulative effect on liver glycogen deposition. The highest level is attained in five days and then slowly declines but does not reach the normal level (41). Further studies by Ingle *et al.* (42) show that eviserated rats given glucose and insulin plus adrenal cortical extract by continuous intravenous injections, show a significant rise in blood sugar. Cortisone and hydrocortisone administered in identical fashion proved to be ineffective.

Bacila & Barron (43) studied the effects of adrenal cortical hormones on anaerobic glycolysis and hexokinase activity. They suggest that adrenal hormones inhibit glycolysis by combining with the -SH groups of hexokinase. Leonard (44) found that glycogen deposition induced in skeletal muscles by cortisone varies considerably for not all muscles respond in the same fashion by glycogen deposition. Epinephrine caused glycogen depletion in rat skeletal muscle but cortisone treatment completely inhibited the glycogenolytic activity of the amine in the rectus femoris muscle but not in the diaphragm (45). Porter & Silber (46) used liver glycogen deposition as a measure of the

rates of absorption of cortisone and hydrocortisone and their acetates after intramuscular and subcutaneous injections. Hydrocortisone alcohol was most rapidly absorbed by either route, and absorption from muscle was speedier than following subcutaneous injection.

The cold stress test for determining the activity of adrenal steroids has proved to be useful as a tool for investigating various aspects of adrenal function. Exposure to cold results in marked increase in fasting ketosis which is depressed by cortisone and hydrocortisone treatment (47). Oral or intravenous glucose administration exerted a protective effect on the response of the adrenal gland in animals exposed to cold (48) and alloxan given to pregnant rats did not interfere with the concentrations of cholesterol and ascorbic acid in the adrenals when the animals were exposed to cold (49).

According to Renold & Hastings (50) there is a difference between pancreatic diabetes and adrenal steroid diabetes in that only increased production of glucose occurs in the liver of cortisone-treated rats, whereas the liver of the diabetic animals also exhibits decreased utilization of glucose. Apparently metabolic differences exist between the two types of diabetes. Ethylenediamine has a diabetogenic effect upon partially depancreatized rats; the glycosuria following administration of this agent is extra-adrenal but can be modified by removing these glands (51).

Muscle work test.—Ingle and co-workers (52, 53) have continued their studies on the effect of adrenal cortical extract and various glucocorticoids upon the work output of adrenalectomized rats under varying conditions. The presence of the liver and other intra-abdominal organs was found not to be necessary for an effect of cortical extract upon muscle work. Continuous intravenous injection of adrenal hormones improved the work output of adrenalectomized-eviscerate rats. Other observations (54) showed that the work performance of hypophysectomized-adrenalectomized rats is not restored to normal by adrenal hormones. However, by adding certain commercial preparations of ACTH[2] to the extract, normal performance was obtained. Some partially purified ACTH material markedly affected work output in the hypophysectomized-adrenalectomized rat.

Type of steroid secreted by the cortex.—Corticosterone and hydrocortisone or a mixture of both are secreted by the cortex in greatest amount in all mammalian species so far investigated. Reports in the literature of the past few years indicate that the adrenals of monkeys and sheep secrete principally hydrocortisone, those of rats and rabbits produce mainly corticosterone, whereas cats, dogs, ferrets, and cows elaborate mixtures of both types of steroid. The glands of man appear to secrete chiefly hydrocortisone and probably small amounts of corticosterone.

The adrenal vein blood of rabbits contains chiefly corticosterone but following administration of ACTH for a week, hydrocortisone as well as corticosterone appeared in the ratio 1:2. If ACTH is injected for long periods, hydrocortisone becomes the dominant steroid present (55). The predominant secretory product in adrenal vein blood of both normal and hypophysec-

tomized sheep is hydrocortisone; small amounts of corticosterone are also present (56). Human ascitic fluid contains hydrocortisone but cortisone may also be present in traces (57).

17-Ketosteroids.—Numerous papers have appeared during the past year concerned with urinary excretion of corticosteroids and 17-ketosteroids and new and improved methods for their detection (58 to 61). Volume 9 of the *Recent Progress in Hormone Research* series, published by the Academic Press, New York (1954), and Volume 7, *Synthesis and Metabolism of Adrenocortical Steroids*, Ciba Foundation Colloquia on Endocrinology, published by Little, Brown & Company, Boston, Mass., contain numerous valuable papers on 17-ketosteroids, corticosteroids, steroids as tracers, etc. The reader is referred to these publications for authoritative discussion on these subjects. Dorfman & Ungar (62) have also published a detailed monograph dealing with the metabolism of the steroid hormones.

New-born infants, from two to five days of age, have a significantly lower level of circulating free hydrocortisone-like substances in the blood than the levels found in older individuals (63). Gemzell (64) found that blood levels of 17-hydrocorticosteroids rose during pregnancy and in the last trimester attained levels four times the normal. Shortly after delivery the steroid level rose to seven times the normal only to fall again by the sixth day.

Adrenal perfusion and steroid metabolism.—It has been shown that radioactive 17-hydroxycorticosterone and corticosterone are produced when C^{14} labeled acetate and labeled cholesterol plus ACTH are perfused through beef adrenal glands (65). Adrenal tumor tissue can utilize sodium acetate-1-C^{14} as a substrate for the synthesis of cholesterol in isolated organ perfusion (66). Meyer *et al.* (67) have reported on the products isolated from the adrenal following perfusion of epiandrosterone. About 33 per cent of this substance was obtained unchanged plus approximately 10 per cent androstane-3,17-dione. Some 11β-hydroxylation was also present. Further studies involving perfusion of the liver of rats and rabbits with various steroids have been made by Hechter *et al.* (68), and Bloch, Dorfman & Pincus (69) reported on the presence of 17-ketosteroids in adrenal perfusates.

The rôle of the liver, kidney, and spleen in removing 17-hydroxycorticosteroids from the blood of rats has been investigated (70). Injections of hydrocortisone produced high concentrations of hormone followed by a rapid fall to low levels. Removal of the liver prevented this decline but nephrectomy and splenectomy had no effect. Burstein *et al.* (71) investigated the γ-ketolic and 17-ketosteroid metabolites isolated from urine of a patient following oral administration of large amounts of hydrocortisone. Reference has been made in the preceding section to Dorfman & Ungar's (62) monograph on metabolism of steroid hormones and to other recently published books on this and related subjects.

Zonation and effects of hypophysectomy on the adrenal.—Long-term hypophysectomized mice show no deviation from normal in electrolyte metabolism. This is attributed to the healthy remnant of the cortex remaining after pituitary removal (72). Injections of ACTH induce regeneration of

a normal appearing cortex from the zona glomerulosa (73). Adrenal demedullated rats with regenerated cortices are able to handle administered water loads, hence the medulla is apparently not important in this respect (74). Rats with diabetes insipidus show a prominent zona fasciculata and zona reticularis but the zona glomerulosa is narrow or else absent. (75) The authors do not believe that the zona glomerulosa controls electrolyte metabolism and ascribe most of the secretions of the cortex to the zona fasciculata.

Lever (76) has made a study of vascular zoning in the cortex and Knigge (77) recently published a detailed report on the effects of hypophysectomy on the adrenal of the hamster. Great shrinkage of the cortex occurs, confined to the fasciculata and reticularis zones. The zona glomerulosa remains histologically normal and the medulla is unchanged. According to Christensen (78), however, the medulla does undergo a certain degree of atrophy after hypophysectomy. Nichols & Green (79) report that, after three weeks' treatment with DDD,[2] the inner zones of the cortex of dogs become atrophic while the outer zones remain unaffected. ACTH injections do not induce eosinopenia, diabetic glucose tolerance curves, or increases in uric acid or allantoin. Since these changes do occur in normal dogs injected with adrenocorticotrophin, the authors conclude that the atrophic zones normally elaborate the hormones responsible for these changes or else the nonatrophic outer zone, under the influence of DDD is refractory to ACTH.

Circulatory changes induced by adrenalectomy and hormone administration.—Recent investigations indicate that the peripheral vasculature may be one locus of action of cortisone and hydrocortisone and that the profound asthenia and loss of reactivity of the minute peripheral vessels is probably a primary causative factor in the greatly enhanced susceptibility of the adrenalectomized animals to stress.

Adrenalectomized rats subjected to anaphylactoid shock revealed that death was attributable to progressive slowing of the peripheral circulation, pooling and sequestration of blood in the capillaries, stasis, and eventual circulatory collapse. Pretreatment with cortisone prevented these reactions (80). The most effective prophylactic for anaphylactoid shock and the companying circulatory failure was found to be aqueous-alcohol solutions of cortisone rather than microcrystalline suspensions (81).

Epinephrine was an effective agent for preventing this type of shock in 24-hr. adrenalectomized rats infused with dextran. The striking resistance of hypophysectomized, as contrasted with adrenalectomized rats, to dextran infusion is attributable to release of epinephrine from the medullae of the atrophic adrenals (82).

Zweifach *et al.* (83) demonstrated that adrenal removal definitely decreases arteriolar tone; the terminal vascular bed undergoes progressive loss of functional activity; vasomotion ceases, and the precapillary sphincters are markedly affected. All of these signs of circulatory failure are completely restored to normal by administering cortical hormones. Barclay & Ebert (84) employing the rabbit-ear chamber, noted, among other things, that

cortisone increased the general vascular tone, and in serum sickness and tuberculosis infections the steroid prevented dilation of the arterioles and lessened the damage to the vascular endothelium.

The rate of blood flow decreases and stasis develops about 24 hr. before death occurs in adrenalectomized hamsters; cortisone and DCA greatly improve the circulation. Cortisone treatment of normal hamsters induced arteriolar constriction, the precapillary sphincters were narrowed, and the arteriolar smooth muscle "maintained a state of firm contraction" (85). Sugiura (86) observed that epinephrine in doses which cause vasoconstriction, failed to do so when the hamsters were given prophylactic foretreatment with cortisone. The steroid modifies the constrictive action of the smooth muscle cells of the peripheral vessels. Beznák (87) has studied the effect of ACTH and cortisone on the lowered heart weight and blood pressure of hypophysectomized rats. They were without influence, but DCA restored the weight of the heart and partially restored the blood pressure. Cortisone pre-injection treatment greatly reduces the increased permeability of the capillaries caused by intradermal injections of tissue extracts (88). Bergen *et al.* (89) found that the reduced blood flow through the brain of adrenalectomized rats can be rapidly restored to normal by cortisone, cortical extract, or Δ^5-pregnenolone, but not with DOC.

The relation of the cortex to histamine has excited interest because some have considered it not unlikely that this substance may be responsible for the circulatory effects resulting from adrenal removal. However, Code *et al.* (90) were unable to find any effect of adrenalectomy on the blood histamine concentration of rabbits maintained with DCA, exhibiting insufficiency or treated with cortisone.

Is the eosinophil test specific for adrenal steroids?—Glucocorticoids will induce eosinopenia in Addisonians, and epinephrine is also effective in this respect (91). Others have observed that the salt-maintained patient with Addison's disease and the bilaterally adrenalectomized human exhibit eosinopenia when injected with epinephrine (92, 93). Conn & Fajans (94) and Pincus & Elmadjian (95) have cited references to these earlier reports. However, the evidence questioning the specificity of the eosinophil test has continued to accumulate.

Adrenalectomized dogs injected with bacterial pyrogens develop marked eosinopenia (96), and epinephrine in large doses is eosinopenic in dogs and human subjects lacking adrenals and in Addisonian patients maintained on cortisone (93). Swingle *et al.* (97) observed striking eosinopenia in adrenalectomized dogs subjected to stress procedures and receiving large doses of certain drugs. Dogs with surgically established arteriovenous anastomoses show significant rises in eosinophils during the morning hours; adrenal removal failed to lower the number of these cells, and an extra-adrenal mechanism was postulated for this morning increase (98). Speirs (99) observed that large numbers of adrenalectomized mice develop accessory adrenal cortices if maintained for protracted periods. Such accessories when stimulated by epinephrine or ACTH are apparently capable of secreting sufficient

C_{11}-oxygenated steroids to induce eosinopenia. Bibile (100) found dog plasma protein effective in producing a fall in circulating eosinophils in adrenalectomized mice. Dumm & Ralli (101) interpret their data as indicating that eosinophil counts can be modified by factors other than the hormones of the adrenal cortex. Occasionally a case of human adrenal insufficiency is associated with profound eosinopenia (102). According to Jenkins *et al.* (103) there exists evidence for extra-adrenal mechanisms of eosinopenia independent of hormones liberated by the adrenal.

The recent work of Speirs (99) on accessory cortical tissue in mice, and the observations of Graham (104) on the prevalence of similar tissue in man raise the question whether the eosinopenia induced in adrenalectomized individuals may not result from release of C_{11}-oxygenated steroids by these accessory bits of cortex. This hardly applies to adrenalectomized dogs since these animals invariably die of adrenal insufficiency within a few days following withdrawal of therapy (97). Despite the fact the eosinophil test may not be specific for C_{11}-oxygenated steroids, it does serve a useful purpose for measuring the responsiveness of the adrenal cortex. This is attested by the numerous investigations which continue to employ it (100, 105 to 114).

Ascorbic acid.—The mean ascorbic acid content of the adrenal cortex of cancer patients before ACTH treatment was 131 mg./100 g. of tissue in males and 139 mg. in females. Twenty-five units of ACTH produced a 32 per cent depletion (115). Adrenal steroids continue to be produced by the adrenals of scorbutic guinea pigs (116), and Wied (117) has called attention to the importance of ascorbic acid for the stress mechanism of rats exposed to cold. Gerschman & Fenn (118) report definite decreases in adrenal ascorbic acid upon exposure of rats to high oxygen tensions. It has been found that hog renin, but not heat-inactivated renin or serum antirenin (119), and salicylamide (120) deplete the adrenal ascorbic acid. This vitamin when fed in excess may prevent the breakdown of cortisone to 17-ketosteroids (121). Dhyse *et al.* (122) have made a study of the vitamin content of liver following adrenalectomy and cortisone treatment. Pretreatment of rats with DCA prevents the fall in ascorbic acid induced by epinephrine. This depletion was obtained as soon in adrenal demedullated as in normal animals (123).

Hypertension, sensitivity to surgical trauma, etc.—Surgical removal of the adrenals for relief of hypertension has become a commonplace therapeutic measure. The particular steroid or steroids presumed to be at least partially responsible for inducing the high blood pressure remain unknown although hydrocortisone has been implicated (124). Study of the new steroid aldosterone may shed some additional light upon this matter.

Bilateral adrenalectomy for relief of malignant and chronic hypertension has markedly beneficial effects in many cases (125, 126). In order to maintain the patients, cortisone, DCA, and adrenal extract are used. Some surgeons prefer to combine the operation of adrenal resection with sympathectomy rather than to rely upon either procedure alone (127). Long-term treatment with large doses of C_{11}-oxysteroids renders patients poor surgical risks

according to Salassa *et al.* (128). They report two cases of postoperative death which they attributed to adrenal insufficiency associated with atrophy of the cortices induced by previous treatment with cortisone.

Many studies on the use of adrenal steroids in the treatment of various disabilities have appeared during the year, but the stricture of space forbids discussing them here. An excellent collection of papers on the mechanism of corticosteroid action in disease processes is now available in book form (129).

THE ANTERIOR PITUITARY

Formed Elements of Blood

The increased interest in the relation of the adenohypophyseal hormones to the formed elements of blood has prompted a separate review section.

Erythrocytes.—Use of radioactive element techniques has revealed that the anemia developing after hypophysectomy in the rat is not associated with a reduction in the life span of the erythrocyte (130). On the basis of previous studies of total circulating red cell volumes employing P^{32}-labeled erythrocytes (131), it was concluded that the hypophysectomized rat produces only 55 per cent of the normal number of erythrocytes. The post-hypophysectomy anemia is directly attributed to the absence of the anterior lobe (132). Growth principle exerts no significant influence upon the concentration of peripheral red cells in the hypophysectomized rat, but it does induce erythroid hyperplasia of the bone marrow (133, 134). Extramedullary and *in vitro* erythropoiesis is also enhanced by the somatotrophic principle (135, 136, 137). The inability of the growth factor to influence peripheral red cell numbers is probably attributable to the increase of plasma volume in the hypophysectomized dog (138) and rat (133).

The feeding of raw anterior pituitary from sheep will repair the anemia of hypophysectomy and induce significant increases in the red cell count of adrenalectomized rats (139). The active factor was recovered in an acetic acid extract of sheep pituitary, was concentrated by oxycellulose adsorption, and was eluted with 0.1 N HCl (140). Daily injections of 100 micrograms produce polycythemia in the hypophysectomized rat (141). The discovery of a specific hypophyseal erythropoetic factor would be of fundamental and practical significance, and its relation to the "erythropoietin" in blood of severely anemic rabbits merits investigation (142).

Leucocytes.—The relation of adrenal steroids to the eosinophil has already been discussed and is here extended to include the trophic factor. Kelley *et al.* (143) failed to correlate the eosinophil response with the 17-hydroxycorticosteroid levels following ACTH and questioned the assumption that the eosinopenia induced by ACTH need be mediated through the steroids. Evidence of extra-adrenal actions of ACTH on the blood elements has been presented (144). A synergistic action for epinephrine in conjunction with ACTH or the 11-oxycorticosteroids on circulating eosinophils has been described in the human (145) and in the splenectomized-adrenalectomized rat (146).

The finding that ACTH-induced eosinopenia may be prevented by pretreatment with trypan blue (147) suggests the reticulo-endothelial system as a site for disposal of the eosinophil. This is in accord with previous reports by Padawer & Gordon (148, 149), who noted increased numbers of degenerated eosinophils, both free and within macrophages, in the peritoneal and pleural fluids of the rat. The eosinophil response to ACTH is not influenced by splenectomy (150, 151), thus eliminating splenic sequestration as a contributory factor in the acute eosinopenic reaction. Possible influences of the adenohypophyseal secretions upon eosinotactic stimuli (151) and diapedesis and migration of eosinophils into tissues (152) remain to be clarified.

A diminished eosinopenic response to ACTH has been reported in the scorbutic guinea pig (153) and in the pantothenate-deficient rat (144). Similarly, pantothenate deficiency in man results in a supression of the lymphopenic response to ACTH (154), suggesting once again a relation between coenzyme A and adrenal steroid metabolism. It is conceivable that the effects of pantothenic acid deficiency may be the consequence of an associated abnormal ascorbic acid metabolism (155). Chronic inanition per se does not account for the diminished eosinopenic response to ACTH (153). It is of interest that pyridoxine deficiency in rats fails to alter the eosinopenia (156).

Bone marrow.—Quantitative studies of the bone marrow in hypophysectomized rats indicate a 40 per cent reduction in cellularity after four months (134). Greater percentages of mature granulocytic forms and of lymphocytes are present (157). The hypoplastic marrow has a decreased respiratory rate (157, 158); glycolytic activity, however, is unchanged (134). Cortisone results in a depression of $Q_{O_2}(N)$ values and decreases the percentage of immature neutrophilic granulocytes of the bone marrow of the hypophysectomized rats (134).

It is generally acknowledged that ACTH, in the acute experiment, exerts little influence on the cellular pattern of the bone marrow of human subjects (159, 160). Increased erythropoiesis and myelopoiesis have been reported in man, under chronic treatment with ACTH and cortisone (161). Fruhman & Gordon (135), employing a method which determines the total numbers of cellular elements within the femoral marrow, have observed marked increases of nucleated erythrocytes and decreases of lymphocytes and eosinophils following chronic treatment with hydrocortisone. Experiments should be directed towards determining the mechanism underlying the ability of ACTH and the adrenal steroids to ameliorate the marrow picture in myelogenous leukemias as well as the explanation for the refractoriness developed after chronic treatment with these agents.

Adrenocorticotrophin

The stimulation of the adrenal via exogenous corticotrophin continues to be a valuable tool of therapy and diagnosis. The isolation and properties of alpha-corticotrophin have been described (162). Studies on the C-terminal

sequence of corticotrophin are being continued (163). The most active ACTH preparations lack isoleucine and threonine (164). A potent steroidogenic ACTH was found to be poor in ascorbic acid depletion (165).

Prolongation.—Further attempts to create a more physiological release of ACTH from a long lasting reservoir have been made. The zinc phosphate-adrenocorticotrophin precipitate and ACTH-beeswax-oil have been reported (166 to 169) with no apparent advantage over other depot-type preparations.

Prolongation by antienzyme protection and inhibition of tissue spreading was effectively brought about by antienzyme-antihyaluronidase agents (170 to 174). The subcutaneous effectiveness of crude ACTH was increased to that of purified, by the inhibition of the self proteinases (175) contained in crude ACTH.

Mechanism of activation.—McCann (176) was able to block rat adrenal stress response and epinephrine-induced eosinopenia by placing a lesion in the median eminence of the tuber cinereum. Adrenal demedullation of rats did not prevent ascorbic acid depletion by stress (177). Massive subcutaneous infusions of epinephrine did not induce histologically detectable pituitary-adrenocortical stimulation (178). Morphine interfered with the epinephrine-pituitary stimulatory mechanism (179). The stimulation by sympathomimetic drugs was blocked by adrenergic agents (180). Although epinephrine and ACTH cause eosinopenia in man, only ACTH increases blood compound F (181). Wolfson found that epinephrine was not a normal physiological pituitary stimulus (182), as did Meyer (183). Epinephrine did not increase 17-hydroxycorticosteroids or 17-ketosteroids (184, 185). Transplacental ACTH was found to be the agent for fetal rat adrenal hypertrophy (186).

Metabolic effects.—Haynes *et al.* found increased hydrocortisone formation by adrenal slices in the presence of ACTH (187). Brummel *et al.* reported that ACTH increased the energy metabolism of adrenal tissue (188). Oxygen consumption under ACTH infusion in experimental shock of the rat was increased 53 per cent, and survival was increased 54 per cent (189). On the other hand, depletion of ACTH protects against damage induced by high oxygen tension or increased atmospheric pressure (190). The adrenal *in vitro* synthesis of steroids was investigated for normal and hypophysectomized rat adrenal under stimulation of ACTH (191). An interesting paper by Kass *et al.* has examined the pattern of corticosteroid production in the rabbit on ACTH stimulation (192).

Adrenocorticotrophin purified with oxycellulose was found to be adipokinetic and to stimulate oxygen consumption in the rat (193). An increase of liver weight in guinea pigs may reflect the adipokinetic action (194). A ketonic effect, not mediated through the adrenal, has reached preliminary report (195).

The biological half life of endogenous ACTH was found to be approximately one minute (196). ACTH, in small quantities, stimulates adrenal

ascorbic acid production (197). Ingle has shown an interesting effect of ACTH on increasing work performance of the adrenalectomized rat (198). The *in vivo* ascorbic acid depletion was duplicated in man in an unusual experiment (199).

There are differences among ACTH preparations which affect their anti-insulin activity and fasting blood sugar effects (200). The response of man, too, may vary for subjective reasons (201). Dobriner did not find that age affected the response to ACTH (202), while Gordon *et al.* feel that the aged and chronically ill showed reduced response when considered in different clinical parameters (203). The analysis of ACTH stimulation from more than one clinical aspect was stressed by Thorn (204).

Electrolyte changes associated with adrenal and pituitary-adrenal stimuli can be controlled by potassium intake (205) without affecting the anti-rheumatic effects (206). Kinsell has urged that symptomatic relief be carried to a point of tolerance (207). The combination of ACTH and cortisone has a synergistic effect for use in chronic illnesses (208).

The relationship between the logarithm of the human intravenous dose of ACTH and urinary ketosteroids follows a sigmoid curve (209). The 8-hr. infusion is satisfactory for a human potency test and to indicate the degree of clinical response (210, 211). The skin darkening of intact frogs has been related to the log of ACTH dose (212). The use of thymus involution was proposed as an assay (213). A method for determination of ACTH in blood of hypophysectomized dogs has been described (214) as also in blood of intact human beings (215). The *in vitro* stimulation of oxygen uptake of adrenal cortex slices from cattle has been suggested for ACTH assay (216) as has an *in vitro* frog skin test (217).

Somatotrophin

Chemistry and properties.—Physicochemical studies (218) and electrophoretic studies (219) continue to indicate the heterogeneity of relatively pure preparations of somatotrophin. Ox somatotrophin was investigated by zone electrophoresis on starch and was found to migrate as a single zone at various pH's (220). Li & Pedersen (221) found, by ultracentrifuge analysis, that the molecular weight was a function of pH as well as ionic species. However, the activity was independent of molecular size. Treatment of purified somatotrophin with glacial acetic acid at 70°C. is reported to result in a loss of activity (222). This is contrary to the findings of Raben & Westermeyer (223). Conciliation between these apparent differences may lie in the fact that the Li group (222) subjected highly purified materials to the glacial acetic acid treatment, whereas the Raben group (223) used a crude anterior pituitary powder. Li & Ash (224), using the dinitrofluorobenzene reaction, suggest that somatotrophin consists of two open peptide chains with alanine and phenylalanine as the N-terminal amino acid residues.

Nitrogen metabolism and growth.—Demonstration of positive effects of growth hormone administered intravenously to normal adult men was de-

scribed by Carballeira *et al.* (225). Blood amino acid nitrogen and urinary amino acid nitrogen levels were lowered and a transient hyperglycemia was observed. The inability of other workers to obtain positive results is ascribed to the possibility that the intramuscular route of administration may result in destruction of the hormone *in situ*.

Kinsell and his group (226) were unable to obtain unequivocal anabolic effects when growth hormone was administered intramuscularly to eight normal humans. Bartlett (227) found growth hormone to alter the effect of androgen upon nitrogen metabolism. According to Beare *et al.* (228), growth hormone was unable to increase body weight or produce nitrogen retention in pyridoxine-deficient rats. Gray *et al.* (229) reported that treatment with growth hormone did not alter the protein distribution of the rat muscle but decreased the adenosinetriphosphatase concentration. Greenbaum & Young (230) studied the effects of growth hormone and starvation on rat muscle and found that the muscles which responded most readily to growth hormone were the same as those most affected by starvation. Scow (231) found no effect of growth hormone on the subnormal muscle/body weight ratio of thyroidectomized rats and only a slight effect on the subnormal muscle myosin content. The catabolic effect of nitrogen mustard could be prevented by somatotrophin (232). Growth hormone did not markedly alter the anabolic changes of cortisone overdosage or vitamin E deficiency (233).

Effects of growth hormone upon the skeletal system are described by Ellis *et al.* (234), who found that the uptake of S^{35} by costal cartilage was markedly reduced in hypophysectomized rats but could be partially restored by growth hormone. Regeneration of the calvarium in hypophysectomized rats occurs with somatotrophin treatment (235). The effect of growth hormone on dentition is ably treated in a series of papers by Baume *et al.* (236, 237, 238).

Beaton (239) described depressed activity of liver arginase and alanine-glutamine transaminase, and decreased urea formation in liver slices from growth hormone-treated adult rats. In the chick embryo it was found (240) that growth hormone caused an increase in the pentosenucleic acids, whereas the desoxypentose nucleic acids were not significantly changed. Kumagai (241) described the effects of somatotrophin upon the lymphatic organs and noted a spleen weight increase.

Carbohydrate and fat metabolism; diabetes.—The inability to separate the diabetogenic factor from growth activity has been reported by Reid (242), who found the diabetogenic/growth activity ratio of preparations of the hormone to be unaltered by treatment with thioglycollate, alkali, carboxypeptidase, or oxycellulose adsorption. When injected at pH 3.5, little diabetogenic activity was observed; however, injection at pH 10 elicited a strong diabetogenic response (243). Houssay (244) has pointed out the diabetogenic effect of growth hormones but made no mention of the pH of the injected material. ACTH enhancement of the diabetogenic action in the intact cat has been reported (245, 246). In the hypophysectomized dog, adrenal cortical steroids prevented growth hormone-induced diabetes (247).

It was postulated that a balance exists between growth hormone and the adrenocorticoids in the regulation of the carbohydrate metabolism of the normal organism. Further observations on the diabetogenicity of growth hormone preparations were described by Mayer & Silides (248) on the genetically obese-hyperglycemic rat. Diabetogenic activity has also been noted in the chick embryo (249). In the diabetic human, Kinsell *et al.* (250) reported accentuation of the diabetes by treatment with growth hormone.

A marked effect of growth hormone upon the pancreas has been described by several investigators. Houssay (244) noted hydropic degeneration of the β cells concomitant with permanent diabetes in the growth hormone treated dog. Comparable results were obtained by Campbell *et al.* (251). Extractable insulin from the pancreas of dogs treated with growth hormone was reduced to from 1 to 2 per cent of normal control values (252). This finding is consistent with other evidence which suggests that, in the dog at least, growth hormone creates an increased metabolic demand for insulin which, in an early stage, increases the rate of secretion of insulin by the pancreas (253). In the rat (254), contrary to what happens in the cat and dog, the size and cytology of the β cells are not affected by growth hormone. Bennett *et al.* (255) presented data to support the view that in the rat and dog growth hormone does not inhibit insulin secretion but may enhance it. Using dog cross-circulation experiments, Foa *et al.* (256) demonstrated the release of glucagon into the pancreatic vein but not into the mesenteric vein of the donor dogs treated with growth hormone.

The metabolic effects of growth hormone in fasting, phlorizinized, and adrenalectomized rats were described by Volk & Lazarus (257). Ellis *et al.* (258) found growth hormone effective in restoring the depleted glycogen content of the tibia of hypophysectomized, immature rats. Similarly, the hormone prevented the depletion of glycogen from cardiac muscle of fasted, hypophysectomized rats (259); Bowman (260) reported a glycostatic action of growth hormone in the muscle of the hypophysectomized female rat.

Greenbaum (261) has studied the effects of growth hormone on fat metabolism in the rat and found an increased body weight with a fall in respiratory quotient; exhaustion of body fat restricted body weight gain. The hormone was found to induce a rapid mobilization of fat in the liver, the peak being reached 6 hr. after injection (262). Liver synthesis of phospholipids was also stimulated. Cornatzer (263) obtained similar results using P^{32} and also found an increase in nucleoprotein synthesis by the liver. In adult female rats, liver fatty acid oxidase, esterase, and acetoacetate production were affected by growth hormone administration with a resultant ketonemia (264). Bondy (265) has also noted ketosis as a consequence of rapid intravenous administration of growth hormone in man and suggests that fat is utilized as the major metabolic substrate.

Miscellaneous.—Selye (266) reported the antagonism of somatotrophin to cortisone-induced involution of the thymus and adrenal cortex in the rat, whereas Spain & Molomut (267) indicated the inability of growth hormone to counteract the effect of cortisone on wound healing. The involution

of lymph glands resulting from x-irradiation was partially inhibited by treatment with growth hormone (268). The mortality of mice exposed to x-irradiation was not reduced by treatment with growth hormone (269). The renal damage caused by a choline-deficient diet was increased by administration of growth hormone. The weight loss occasioned by this deficient diet was not prevented by the hormone (270). Friedman *et al.* (271) were unable to obtain renal hypertrophy and hypertension in the rat treated with growth hormone. Retention of K, Na, Cl, and N in adrenalectomized rats, as a result of treatment with growth hormone, is reported by Stein *et al.* (272). The effect on the mortality, litter weight, and endocrine organ weights of pregnant rats treated with purified growth hormone has been described (273).

Reinhardt & Li (274) have produced chronic arthritis with bony changes by administration of growth hormone to adrenalectomized and ovariectomized guinea pigs over a period of several months. Sawyer (275) has found serum cholinesterase levels of hypophysectomized rats to be depressed by growth hormone. The relation of growth hormone to tumorigenesis was reviewed by Reid (276).

Thyrotrophin

D'Angelo (277) has correlated pituitary and blood thyrotrophin concentrations with cytologic changes in the anterior pituitary of propylthiouracil-treated guinea pigs. The basophil histology and activity are directly related to pituitary thyrotrophic level.

The wise choice of the guinea pig has made possible the demonstration of increased pituitary thyrotrophin content under conditions resulting in sustained high blood levels of the trophic hormone (277, 278) and associated pituitary basophilia. The histologic localization within the anterior pituitary of the three types of glycoprotein-containing cells (basophils) has been described (279). The basophils responsible for thyrotrophic secretion were found in the central and posterior regions of the anterior lobe. Preliminary electron microscopy studies of pituitary by Farquhar & Rinehart (280) suggest separate types of basophils for gonadotrophic and thyrotrophic secretions.

Iodide trapping.—The capacity of the thyroid to "trap" iodide was increased in the hypophysectomized rat given thyrotrophin when the thyroid iodine concentration was low (281). An iodine-deficient diet in the normal rat resulted in elevated thyroid/serum (T/S) iodide ratios and an increased thyroid iodide trapping capacity, without histologic evidence of enhanced thyrotrophic secretion (282).

Evidence for the influence of the level of iodine intake in the absence of thyrotrophin was found in the hypophysectomized rat on an iodine-deficient diet: the T/S iodide ratio was higher than in the hypophysectomized rat on normal iodine intake without change in thyroid morphology (282), and the thyroidal I^{131}-uptake increased with some evidence of thyroid ac-

tivation (283). Further, Halmi (282) found exogenous thyrotrophin was more effective in raising the T/S ratio in the hypophysectomized rat when the iodine intake was low, but the latter did not potentiate the effect on thyroid morphology. Pituitary-hypothalamic interruption (284) or intraocular pituitary implants in hypophysectomized mice (285) allowed near-normal iodine metabolism but did not permit normal thyroid growth.

Metabolism.—The thyrotrophic content of the blood was increased after thyroidectomy (286), cold (278), and propylthiouracil (277). The combination of cortisone and goitrogen augmented the blood and pituitary thyrotrophic changes compared to the effect of propylthiouracil alone (287). The rate of disappearance from the blood of exogenous thyrotrophin was found by D'Angelo to be much greater in the normal than in the hypophysectomized (288) or goitrogen-treated (289) rat.

In the guinea pig, the rate of biological decay of thyroid I^{131} was accelerated by thyrotrophin (290). When thyrotrophin was injected into the chorioallantoic membrane the time of radioiodine uptake by the thyroid was not altered, but the magnitude was increased (291). Significant amounts of injected labeled thyrotrophin were found in the thyroid, gonads, and liver (292).

Pituitary-thyroid changes following goitrogen withdrawal have been reported for the guinea pig (293). Blood thyrotrophic concentration decreased gradually, while thyroid I^{131} uptake increased greatly during the two weeks immediately after withdrawal.

Fright thyrotoxicosis in the wild rabbit did not involve the pituitary-adrenal axis; an increased thyrotrophic secretion with ACTH inhibition was suggested by Kracht (294). In the goitrogen-treated rat Freedman & Gordon (295) found the increased thyrotrophic output did not impair the pituitary-adrenal response to acute cold stress. Hypophysectomy or thyroidectomy decreased tooth eruption rate in infant rats (237, 238).

In euthyroid patients thyrotrophin caused a decreased urinary excretion of I^{131} (296) and a rise in I^{131} uptake (297); in primary myxedema these changes did not occur. In contrast, in pituitary hypothyroidism the trophic hormone caused responses similar to those obtained in euthyroidism (296, 297). Thyrotrophin in the normal thyroid patient gave rise to a syndrome resembling exophthalmic goiter without exophthalmos; in nodular nontoxic goiter a temporary nodular toxic goiter developed (298). The uptake of I^{131} was stimulated by thyrotrophin fifty-four days after an initial therapeutic dose of radioiodine (299). Administration of thyrotrophin to patients with and without thyroids for up to three weeks did not produce exophthalmos (300).

Miscellaneous.—When a purified preparation of thyrotrophin was subjected to papain digestion, a biologically active, dializable, material not precipitated by 20 per cent trichloroacetic acid was obtained by Fels *et al.* (301). Differential solubility in 8 per cent trichloroacetic acid separated exophthalmic-producing and thyroid-stimulating activities; the former was

assayed in *Fundulus*, the latter in day-old chicks (302). Ion exchange chromatography was used to purify crude thyrotrophin (303).

The thyroidal uptake of I^{131} in the intact rat pretreated with iodinated casein (304) and the depletion of iodine from chic thyroids (305) have been used for thyrotrophic assay.

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THE PANCREAS, INSULIN, AND GLUCAGON[1,2]

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The endocrine and exocrine portions of the pancreas have continued to be subjects for intensive study. While formerly their functions have been considered to be separate, more recently it would appear that their activities are correlated, to some extent, through other endocrine glands (1, 2, 3). In this review only the endocrine portion of the pancreas, insulin, and glucagon will be considered.

The endocrine pancreas consists principally of the islets of Langerhans scattered diffusely through the acinar tissue. These islets are rather labile structures whose mass and appearance change according to alterations in the insulin requirements (4). The distribution of the various cell types in the islets of different species has been recently reviewed (5) and the development of the islet cells described (5, 6). Using stains which allow the observation of Golgi apparatus and mitochondria, Bencosme concluded that α and β cells develop independently and throughout life remain separate. At no time was there evidence of transformation of acinar to islet cells (6). Others have expressed the opposite view (7, 8). The objections to acino-insular transformation reviewed by earlier workers (9) still hold.

The arteries which supply the pancreas in the rat have such efficient anastomoses that necrosis in the area of their individual distribution does not follow interruption. The blocking of three or more of the arteries to the pancreas, however, leads to vacuolation and degranulation of α and β cells, but later the islets in areas free from necrosis are increased in number but decreased in size (7). A number of recent reports have again shown the parallelism between the granulation of the β cells and the insulin content of the pancreas (10, 11, 12), and in one, a highly significant linear correlation between the density of β cell granulation and the concentration of extractable insulin in the pancreases of diabetic and of nondiabetic subjects was demonstrated (12). The regranulation of the β cells has again been described after the granules had disappeared as a result of injections of insulin (11). The histochemically demonstrable sulfur of the β cells has been proposed as a means of estimating the concentration of insulin which they contain, on the assumption that all of the sulfur is present in the insulin (13).

The islet mass.—Brief reviews of factors influencing islet volume have been published (4, 14). The islet mass of the pancreas increases with age, as

[1] The survey of the literature pertaining to this review was completed in May, 1954, and only a few subsequent references have been included.

[2] The following abbreviations have been used in this chapter: ACTH (adrenocorticotropin); DCA (desoxycorticosterone acetate).

does also the insulin content of the pancreas. It has been suggested that this may be attributable in part to vascular changes (7), but this may be questioned because of the importance of a number of other factors. The total extractable insulin of the pancreas in growing human subjects increases with age, reaching the adult level between the twelfth and seventeenth years. The concentration of insulin in the pancreases of growing nondiabetic human subjects is higher than in adults (15 16).

The main known factors influencing islet activity and growth are dietary and hormonal. Caloric intake has been shown to be important in determining the volume of the islets. If the intake of a balanced diet was reduced sufficiently that the animal did not gain weight, then the islets also failed to grow (17). When equicaloric supplements of carbohydrate, protein, or fat were added to this basal diet, then animals which received the carbohydrate and protein supplements showed a significant increase in islet tissue, whereas those receiving the fat supplement did not (4). The effect of certain dietary factors on the volume of the islets of Langerhans was reviewed earlier by Tejning (18).

That carbohydrate has a stimulating effect on the islets is shown by the results of the continuous intravenous infusion of glucose. This leads to greater than normal growth of the islets, as was known earlier and was recently substantiated and reviewed (19). Rats continuously infused intravenously with glucose for 6 to 14 days, showed a large increase in islet tissue when compared with saline-infused controls. The suggestion was made that the stimulation of the islets was related more particularly to the total amount of carbohydrate administered rather than to the level of sugar in the blood (19). Brown *et al.* (20) found that when part of the pancreas in the dog was locally infused through its artery, systemic hypoglycaemia occurred and islet changes resulted. Some islets showed hyperplasia, others degranulation, and occasional islet cells were hydropic. This very interesting paper provides evidence for a direct stimulation of islet activity and growth by glucose. These authors conclude that insulin and the level of blood sugar are both important factors influencing the activity of the islets.

Hausberger & Ramsay (21) as others previously, found that the intravenous injection of glucose diminished the granulation of the β cells. They observed, however, that when insulin was given before and during the infusion the reduction of the β cell granulation was lessened or prevented, even though there was a similar elevation of blood sugar level. They concluded that not only blood sugar level but also the level of blood insulin governs the secretion of insulin by the β cells.

Nerenberg (22) found that the subcutaneous injection of monosaccharides which could be transformed into glucose stimulated the formation of granules in the islets, whereas, unless digested, disaccharides did not. Glucose injections in rats on a diet deficient in cystine were reported to lead to hyperglycaemia and to hyperplasia of the islets along with degenerative changes. Another paper suggested that the level of glucose in the blood influenced the

sensitivity of the β cells of the islets to the damaging effect of alloxan. Administration of glucose was protective whereas the administration of insulin had a sensitizing effect (23).

The effect of insulin on the islets.—In rats, injections of relatively large amounts of insulin over a considerable period of time had an inhibitory effect on the growth of the islets of Langerhans, though not on the growth of the pancreas as a whole (24). The reported effects of insulin on the islets are reviewed in this paper. The well-known degranulation of β cells with insulin administration has been observed again and the regeneration of the granules following cessation of the injections has been noted (10, 11). When insulin was given over a period of time in sufficiently large amounts, the depression of its production and secretion by the islet cells was sufficient to result in a temporary diabetic state (4, 10).

The anterior pituitary gland and the islets.—The removal of the pituitary gland prevents the growth of the islets of Langerhans though it does not cause a significant atrophy of the islets (25). However, the acinar tissue is greatly reduced, and hence there is a great increase in the concentration of islet tissue in the pancreas, a fact which must be considered when attempts are made to determine islet changes by examining representative histological sections of the gland or by determining islet to acinar ratios (25). One report indicates that, in guinea-pigs, there is a transient change in the islets in the first few days following hypophysectomy (26).

The increase in islet tissue in the intact rat occasioned by daily injections of crude saline extracts of the anterior pituitary gland has been confirmed recently, and a similar effect noted in hypophysectomized animals (27). In mice, age influenced the effect of pituitary extracts on the islets, there being an islet-increasing effect in young, but not in older, mice (28).

The injection of a number of different, highly purified growth hormone preparations also increased islet weights in hypophysectomized and intact rats (27). As with the crude saline extracts, the increase in islet weight was proportionately greater than the increase in body weight in intact rats but not in hypophysectomized animals. Abrams *et al.* (29) report that a growth hormone preparation which increased body weight in rats force-fed a moderate carbohydrate diet, did not affect the β cells nor alter the size of the islets. These authors found, however, that a corticotropic pituitary preparation increased the size of the islets and led to enlargement and degranulation of β cells. This was accompanied by a transitory glycosuria and cytological evidence of stimulation of the β cells. This paper does not support the hypothesis that growth hormone stimulates the β cells. However, another report indicates that the administration of growth hormone in partially depancreatized rats was associated with new islet cell formation and, after a transient increase, a reduction in glycosuria. Administration of ACTH[2] led to further deterioration of the islets and enhanced the diabetes (30). Other work demonstrated that ACTH caused an increase in islet weight in hypophysectomized and intact animals. In the intact rats the effectiveness of ACTH was greatly

enhanced when it was given by continuous intravenous infusion (31, 32). The dosage and manner of administration are important factors in the effect of ACTH on the islets. In both normal and alloxan-diabetic rats, the mitotic activity made evident by colchicine was increased greatly by the administration of pituitary growth hormone preparations and ACTH (33). The growth hormone preparations were said to affect mainly the α cells, while ACTH had its chief effect on the β cells. Prolactin is another pituitary material which has been reported to stimulate the growth of the islets of Langerhans, under some circumstances, in intact (28) and hypophysectomized animals (4). There is no proof as yet that there exists a direct stimulating action of the anterior pituitary on the pancreatic islets. The pituitary preparations do have effects outside the pancreas, however, which increase the endogenous insulin requirements.

In partially depancreatized (34) and intact dogs (35), the administration of highly purified growth hormone preparations was shown to produce permanent diabetes. This was accompanied by a reduction in the islet tissue and severe degeneration of the β cells. This effect was obtained also in the absence of the thyroid gland (34). The insulin extractable from pancreas was very low except in those animals resistant to the diabetogenic action of growth hormone (35, 36). The diabetogenic effects of growth hormone are reviewed by Young (37). The adrenals seem to have an important influence on the diabetogenic activity of growth hormone (38, 39). While most reports indicate an enhancement of the diabetogenic activity of growth hormone by adrenal stimulation one report showed a prevention of the diabetogenic action by adrenocortical steroids (40).

The adrenals and the islets.—Stimulation of the adrenal glands either directly or indirectly by way of ACTH administration leads to an increase in islet tissue as mentioned above. When large doses of cortisone acetate were injected into guinea pigs glycosuria was observed. This was not permanent. The islets showed tremendous hypertrophy with signs of exhaustion of β cells (41). In the rat, too, a temporary diabetes was produced by daily injections of cortisone. The pancreas showed hyperplasia of the islets and new formation of β cells (42). The injection of cortisone in both hypophysectomized and intact animals led to an increase in islet weight (31). The administration of the adrenal steroids A, E and F but not DCA[2] had a protective effect in some partially-depancreatized ovariectomized rats and, in these, led to hyperplasia of the islets of Langerhans (43). In nondiabetic children receiving ACTH therapy the extractable insulin of the pancreas was found to be elevated (44).

The thyroid gland and the islets.—The thyroid gland has a profound influence on islet growth as well as on the growth of the pancreas as a whole. Thyroid administration in the rat reduced the incidence of diabetes following extensive partial pancreatectomy and led to enlargement of the islets and to new islet formation (45). The administration of sufficiently large amounts of desiccated thyroid gland to intact and hypophysectomized rats

resulted in an increase in the weight of the islets of Langerhans, and also in the islet weight per unit of body weight (4). Degranulation of the islet cells and an increase in the β to α cell ratio was reported to result from thyroxine administration (46).

The gonads and the islets.—Gonadectomy was found to have no significant effect on islet weight but repeated daily injections of estradiol benzoate, diethylstilbestrol, and progesterone caused the weight of the islets of Langerhans to be elevated and the islet weight per unit of body weight to be increased. Injections of testosterone occasioned no change in islet weight (47). It would appear that the gonads exert no indispensable influence on islet growth but that under some conditions certain female sex hormones can stimulate the islets and increase islet growth in intact rats. This investigation substantiated the conclusions from previous reports of effects of estrogens on the islets, which have been reviewed recently (48, 49, 49a). Other work is in accord with this (14). A number of estrogenic materials have been shown to afford some protection against diabetes, and in alloxan-diabetic animals the administration of estradiol along with insulin had a curative effect which appeared to be associated with some islet hyperplasia (48). There is one report (50) of a patient with acromegaly accompanied by diabetes in which estrogen therapy resulted in the return of glucose tolerance to normal and alleviation of the diabetes.

The effects of pregnancy on carbohydrate metabolism have been reviewed (51). Both in experimental animals and in man, an increase in islet tissue was found in the pancreases of infants of diabetic mothers and of "prediabetic" mothers but was uncommon in infants of nondiabetic mothers (51, 52, 53). The increase in islet tissue was closely related to body weight (53). Some claim there is little evidence that the increase in islet tissue is compensatory to a lack of maternal insulin or to hyperglycaemia in the mother (53). The islet tissue appears also to be increased in some patients with erythroblastosis fetalis (54).

Zinc and the islets.—A number of substances have been found to affect the islets of Langerhans adversely. The effects of alloxan have been reviewed recently (55, 56) and will not be considered here. The production of pancreatic islet lesions by dehydroascorbic acid and by zinc-precipitating agents such as oxine and dithizone (diphenylthiocarbazone) is reviewed by Wachstein (57). The production of diabetes in rabbits with 8-hydroxyquinoline originally demonstrated by Kadota was confirmed (58, 59), but this effect could not be demonstrated in rats, hamsters, guinea-pigs, cats, or dogs. Rats were protected from the development of dehydroascorbic acid diabetes by the prior administration of atropine (60). Recently it has been reported that the intravenous injection of dehydroascorbic acid in rabbits did not produce diabetes (61).

A decrease in the zinc content of the islets and an increase in zinc excretion in the urine resulted from the injection of dithizone in rabbits (62). A transient reduction in the zinc of the islets accompanied the hyperglycaemia

following the injection of epinephrine (Adrenaline) (63). A study of the distribution of zinc and insulin in the pancreas of teleost fish reveals that the concentration of zinc is much higher in the islets than in the acinar tissue, but only 3 per cent of the weight of islet zinc could be represented as being bound to extractable insulin (64). The administration of radioactive zinc weekly for a six-month period to rats was observed to lead to no damage to the islets of Langerhans and no change in the level of blood sugar (65). Similarly, the intravenous administration of radioactive zinc to rabbits twice a week for 3 months produced no damage of the islets of Langerhans and no increase in blood sugar (66). Lowry, Baldwin & Harrington (67) reviewed the literature on zinc and the pancreas and reported also that after intraperitoneal injection the pancreases of diabetic rats showed lesser concentrations of radioactive zinc than those from normal animals. The possible relationship of zinc to the hyperglycaemic effect of glucagon will be discussed later.

The islets, insulin, and diabetes.—The pathology of diabetes in the human has been reviewed and the prominence and significance of hyaline deposition in the islets as a lesion in human diabetes has been emphasized (68, 69, 70). Monographs and reviews dealing with the islets and their relation to diabetes have recently been published (5, 70, 71, 72).

Studies on the extractable insulin of pancreas in nondiabetic human subjects showed that the concentration was highest in the tail portion and lowest in the head of the pancreas. The concentration of insulin in the pancreas was computed to be approximately 1 per cent of the islet tissue. Despite large variation in the weights of the pancreases of individuals of comparable size the total amount of extractable insulin was relatively constant (16). In two spontaneously diabetic dogs the extractable insulin of the pancreas was found to be less than 2 per cent of controls and somewhat higher in two other spontaneously diabetic animals (73). In 11 human subjects dying with growth-onset diabetes, as in the spontaneous diabetes of four more dogs, the insulin of the pancreas and the number of β cells had reached and remained at very low values within a month of the diagnosis of diabetes for the dog, and within a year for man (74). The early and profound fall in the insulin of the pancreas and reduction in the number of β cells in growth-onset diabetes were not found in a majority of subjects whose diabetes was diagnosed after the age of 23 years (maturity-onset diabetes). The values for the insulin of the pancreas in these subjects covered a wide range from very low to above the average value for nondiabetic subjects. The average insulin of the pancreas in all age groups of maturity-onset diabetic subjects was about 50 per cent of that for nondiabetics and showed little tendency to decrease during the course of the disease. The underlying cause of the diabetes in those subjects with relatively large depots of pancreatic insulin remains unestablished. A general review concerning the insulin content of the pancreas was presented recently (75).

The islets in relation to hypoglycaemia.—The reports of patients with hypoglycaemia resulting from islet cell tumors are too numerous to list here.

This subject has been reviewed by Whipple (76) and others (5, 77). In the pancreases of human subjects with active islet-cell tumors causing hypoglycaemia the β cells outside the tumors have been found to have reduced granulation (78). Similarly in five of six cases with unexplained hypoglycaemia the concentration of insulin in tumor-free portions of the pancreas was below normal (16). Ferner (5) described the cytology of islet adenomata and noted an increase in α cells and hyperplasia of the ducts which he suggested might be compensatory. In harmony with this was the reported increase in α cells of the islets of guinea-pigs following the administration of adequate amounts of insulin over a period of time (79).

Progressive muscular atrophy with increased myotatic irritability (80), degeneration of ventral horn cells, and fatal encephalopathy (81) have been reported in association with islet-cell tumors. The question of cerebral disease attributable to functioning islet-cell tumors was discussed by Richardson & Russell (82).

Confirming previous reports, which were reviewed, alloxan given to patients with islet-cell tumors had no apparent damaging effect on the tumor cells (83). Adrenocorticotropin and cortisone seemed to prevent the hypoglycaemia accompanying islet cell adenomata (84, 85, 86), but in patients with adenomata, growth hormone administration had a negligible short term effect on the blood sugar level (87) even after the pancreas was removed (86). Islet adenomata are sometimes associated with adenomata in several other endocrine glands (88). One author points out that in certain anxious diabetic patients, reactions simulating the effects of hypoglycaemia may occur as a result of hyperventilation (89).

Insulin, the Beta Cell Hormone

Many monographs and abstracts of symposia concerning insulin have appeared recently (37, 90 to 96). A detailed review of "Current Concepts of the Action of Insulin" by Stadie (97) makes it unnecessary to include some sections of that subject. Somewhat different aspects were reviewed by Chaikoff (98) and discussed by Soskin & Levine (99). The monograph on "The Action of Insulin" by Haugaard & Marsh (100) while very comprehensive, does not attempt a detailed critical analysis of individual papers. Mention must be made of other important reviews (93, 101 to 108). Comprehensive discussions of many physiological processes which are affected by insulin are recorded in the 5th Brookhaven Symposium under the general title of Major Metabolic Fuels (109).

New preparations, standards, and assay.—The place of crystalline protamine zinc insulin in the series of new, long-acting insulins is still being studied (110 to 113). It has been found (91, 114, 115) that the phosphate ions used in protamine zinc insulin influence the physicochemical relationship between the constituents. Insulin crystals with increased zinc content are insoluble at neutrality. The addition of phosphate eliminates the prolonged effect of a suspension of these zinc insulin crystals, presumably by elimination

of the zinc as insoluble zinc phosphate, thus permitting the insulin protein to dissolve. Utilizing these reactions in acetate buffer it is possible to prepare products with different durations of effect. Three of these with effects lasting 18 to 30 hours were tried in many clinics (116 to 125). Comparisons of the duration of activity of various forms of insulin have been made (121, 126). When regular insulin was heated for a short time in aqueous solution with urea or methylurea the product was observed to give prolonged effects in animals and man (127). This preparation, which produced a delayed effect even when injected intravenously, was prepared for testing by Eli Lilly and Co. Duncan (112) gave an excellent general statement on the various insulins.

The third International Standard of Insulin has now been established (128). The first standard was an amorphous preparation containing 8 units per mg.; the second was crystalline with a potency of 22.5 units per mg. The present one has been compared by the mouse-convulsion and the rabbit crossover methods with the second standard. The potency of the present standard has been placed at 24.5 units per mg., i.e., one unit is contained in 0.0408 mg. of the third International Standard preparation (1952). A provisional British standard for globin zinc insulin has been set up (129) but this cannot be described directly in terms of the crystalline International Standard since they cannot be assayed under the same conditions.

Chromatographic procedures for the estimation of both protamine and insulin in protamine zinc insulin have been outlined (130). An immunological method has been described for detecting microgram amounts of insulin in pure solution (131). Distribution of error in the assays of regular insulin by the mouse method has been discussed by Young & Stewart (132). Attempts have been made to estimate the levels of insulin in the blood plasma using hypophysectomized, alloxan-diabetic, adrenalectomized rats (133) and the glucose utilization of the isolated rat diaphragm (134 to 137). This latter method has been critically investigated and the effects of insulin antagonists considered. Reported results using these two different methods are sometimes unsatisfactory and not consistent. Values much higher than those reported by Bornstein have been obtained (135).

Administration of insulin.—The rate of absorption of regular insulin applied percutaneously combined with hyaluronidase was so variable and unpredictable that the method was considered unsatisfactory (138). When pellets of insulin containing 100 times the daily dose were implanted in depancreatized or alloxan-diabetic dogs, the blood sugar was reported to be maintained at approximately normal levels for 1 to 2 months (139). A comparison has been made of the intravenous and subcutaneous injection of insulin in diabetic and nondiabetic patients (140). The greater rapidity of onset of the effect after intravenous administration justifies the use of this route in diabetic coma and circulatory shock in the diabetic patient. Addition of hyaluronidase to regular insulin enhanced the hypoglycaemia (141) and prevented the appearance of insulin atrophy in three suceptible cases (142). Changes at the site of insulin injection have been discussed (143).

Sensitivity or resistance to insulin.—A large portion of the literature on insulin might be reviewed under this heading since it could include all interrelationships with the pituitary, thyroid, adrenals, sex hormones, and glucagon. Many of these interrelationships have been considered by Stadie (97) and by Haugaard & Marsh (100). Limitation of space will not permit mention of the many clinical reports on insulin-resistant cases, but Lukens (144) refers to certain aspects of this field.

The finding by Himsworth that individuals can be classified as being either sensitive or insensitive to insulin has been confirmed by the use of glucagon-free insulin (145). Serum from insulin-resistant patients contains greatly increased amounts of substances which interfere with the ability of insulin to stimulate glycogen synthesis in the isolated rat diaphragm (146). This material appears to be associated with the gamma globulin fraction (147) and may prove to be a specific antibody. Glucose uptake by the diaphragm is inhibited by serum from alloxan-diabetic rats; this inhibition is relieved by insulin, by adrenalectomy, and by hypophysectomy. Injections of both cortisone and growth hormone in the diabetic, hypophysectomized animal are necessary to produce the inhibitory property of the serum. Their addition to the diaphragm *in vitro* is ineffective whereas the effect of insulin may be obtained (148). The insulin-reversible inhibition of glucose uptake is associated with the β_1-lipoprotein of the serum of the diabetic rat. Serum from the normal rat or human or from hypophysectomized, diabetic rats did not yield an inhibitory fraction (149). These interesting results await confirmation.

After section of the hypothalmic pathways to the brain stem and removal of the adrenal medulla, rats became resistant to the action of insulin, and its blood sugar lowering effect was not observed. This was so, even after a period in the cold (150). Neither the section nor the adrenalectomy alone led to this resistance. The author suggests that the resistance was the effect of an insulin antagonist. De Bodo & Sinkoff (151, 152) found that epinephrine was not an essential factor in the regulation of carbohydrate metabolism in the dog and that the C-11,17-oxycorticosteroids are perhaps more important than growth hormone in raising blood sugar and antagonizing the hypoglycaemic action of insulin. More recently (153), working with adrenalectomized-hypophysectomized dogs maintained with DCA they have obtained evidence that the adrenocortical steroids are not essential for the anti-insulin action of growth hormone. Lazarus *et al.* (154 to 158) have continued their studies on the use of the modified glucose-insulin tolerance test in diabetic patients and the factors which cause the blood sugar to rise again after a small dose of insulin ("hypoglycaemia responsiveness"). The authors conclude that the stimulus for this response is the low blood sugar itself which elicits a glycogenolytic response in the liver, the level at which this occurs being determined by the endocrine balance.

One interesting report is that of Burns *et al.* (159) who compared the response to glucose and to insulin of healthy medical students and of hospi-

talized patients with acute or chronic illness. The response of ill and healthy subjects to the dose of insulin was essentially the same. Pretreatment with a single dose of cortisone produced a greater loss of insulin sensitivity in ill than in healthy subjects. Their findings suggest that milder degrees of insulin resistance may be detected only in the presence of a glucose load, i.e., the glucose-insulin tolerance test may be a more sensitive indicator of insulin resistance than the insulin tolerance test. A significant loss in insulin sensitivity was observed in only 4 of 17 patients treated with ACTH (160). The insulin sensitivity in patients with pituitary and thyroid disease has been investigated (161), and rapid intravenous glucose tolerance tests have been compared in normal men and patients with hyperthyroidism (162). Insulin hypoglycaemia had a desensitizing effect on certain allergic reactions in guinea pigs (163). Dogs became relatively sensitive to insulin when treated with 1,1,-dichloro-2-2-bis(*p*-chlorophenyl)ethane (DDD). This produced atrophy of the zona fasciculata and zona reticularis of the adrenal cortex similar to that resulting from hypophysectomy (164). Adult rats exposed to cold stress for six days exhibited hyperglycemia, hypersensitivity to insulin, and signs of increased adrenal cortical activity (165).

Scorbutic monkeys were reported to be resistant to insulin, this resistance being referable to an increased elaboration of adrenocortical hormones (166). The administration of ascorbic acid was found to enhance the tolerance to insulin of cortisone-treated adrenalectomized rats and of adreno-demedullated animals treated with ACTH, but did not affect the insulin tolerance in the intact animal (167). The effects of ascorbic acid on insulin sensitivity in the rat have been reviewed (168). The administration of ascorbic acid in intact normal and demedullated rats led to no significant change in blood sugar level, but did give a greater sensitivity to previously injected insulin (168). Animals receiving a low salt diet were less sensitive to insulin than those receiving a normal amount of salt, and DCA-treated animals showed hypersensitivity to insulin (169).

The hereditary hypopituitary dwarf mouse was found to be extremely sensitive to insulin (170). Obese mice which were consistently hyperglycaemic had an increased number of apparently enlarged islands of Langerhans and were resistant to injected insulin (171). The enzyme system which destroys insulin has received further study (172, 173, 174).

Localization of injected insulin.—When insulin, labelled with radioactive sulfur or iodine, was given to intact dogs and rats, it was found that its distribution differed from that of iodinated albumin or free sulfate. Liver and kidney appeared to have the greatest ability to concentrate the material, with little entering the brain (175). Using insulin labelled with radioactive iodine, it was found that when the material had concentrated in the liver it was difficult to remove it by perfusion. In this, it differed from thyroxine (176).

Insulin and potassium.—The fall in plasma potassium after the injection of insulin, epinephrine, or desoxycorticosterone has been studied (177 to

180). The increase in sugar excretion of diabetic rats associated with ACTH administration was inhibited by diets high in KCl (181). There are many clinical papers on the relationship of insulin to potassium metabolism. Kinsell (182) discussed the interesting postulate that loss of potassium was responsible for the resistance to insulin produced by ACTH and cortisone, since giving potassium to the patient restored the sensitivity to insulin.

Epinephrine, nor-epinephrine, and insulin.—A tenfold increase in urinary epinephrine excretion was found in healthy subjects given insulin; the nor-epinephrine excretion was slightly lowered (183, 184). The epinephrine and nor-epinephrine content of human blood and of the adrenal glands of the cat have been measured during insulin hypoglycaemia (185, 186). Insulin caused the adrenal gland to be depleted of epinephrine while the nor-epinephrine content was unchanged, suggesting that epinephrine is a specific metabolic hormone (186).

Miscellaneous effects of insulin.—Pentobarbital anaesthesia inhibited the action of insulin on the utilization of glucose and formation of glycogen in the isolated rat diaphragm (187). Small doses of insulin have been reported to increase the tolerance of dogs to prolonged pentothal anaesthesia (188).

The utilization of glucose, as measured in a closed-circuit Ringer-perfused preparation of the rat heart was increased by insulin (189). Insulin was found to increase the transport of labelled phosphate into the rat diaphragm and to increase the oxidation of C^{14}-labelled glucose and the deposition of glycogen without any effect on the oxygen consumption of the tissue (190). However, insulin was reported to increase the O_2 uptake of muscle from diabetic rabbits (191).

The glycogen concentration and glucose output of rat kidney slices were increased in diabetes and reduced to normal or below by the administration of insulin (192). The effect of insulin on the maximal rate of renal tubular uptake of glucose was studied in patients free from renal and cardiovascular disease and without evidence of derangement of carbohydrate metabolism (193). The diuresis produced by the intravenous administration of glucose or mannitol was counteracted by insulin, but no antidiuretic effect of insulin was seen in subjects with water diuresis (194). Studies on guinea pigs indicated that insulin probably did not affect the permeability of the intestinal mucosa but that its action on the level of the blood sugar accounted for any alteration in absorption from the intestine (195). Studies on the action of insulin in depancreatized dogs (196) support the hypothesis (197) that insulin promotes enzymic processes connected with the passage of sugar through the cell membrane. In experimental diabetes the liver cocarboxylase content, and in clinical diabetes the blood cocarboxylase content, were observed to be decreased, and the mechanism by which insulin affects the phosphorylation of thiamine was studied (198, 199). The stimulating effect of insulin hypoglycaemia on gastric secretion has been further investigated and reviewed (200, 201).

While previous reports would indicate that intravenous injection of insu-

lin into ruminants leads to a reduction in the blood sugar level without typical hypoglycaemic signs, recently it has been found (202) that relatively small doses of insulin injected subcutaneously into adult sheep were followed by long periods of hypoglycaemia terminating in severe and prolonged convulsions. Denervation of the adrenal glands rendered the adult sheep sensitive to insulin given intravenously. Removal of the pancreas in sheep was not followed by any signs of diabetes (203). Other interesting observations on ruminants have been reported (204 to 207). The effects of insulin in normal mammals, birds, and cold-blooded vertebrates have been reviewed (208). Of those species investigated, mammals appear to be most sensitive to insulin, birds most resistant and amphibia intermediate in sensitivity.

The insulin-like action of growth hormone.—Earlier work on the hypoglycaemic effects of growth hormone by Milman and Russell and others was followed by isolation of an anterior pituitary fraction possessing a blood-sugar-lowering property (209). In adrenalectomized animals this fraction appeared to antagonize the action of insulin. Findings of O. Sirek of this laboratory, in depancreatized dogs, suggest that residual "bound" insulin may play an important part in this hypoglycaemic effect. Increased glucose utilization by diaphragm from normal but not diabetic rats was produced by growth hormone and led to the suggestion that the growth hormone liberated insulin held inactive in the tissues (210, 211). If the animal had a blood sugar over 150 mg. per cent at the time of sacrifice, no insulin-like effect of growth hormone was observed. Glucose utilization in the rat diaphragm was depressed by small doses of growth hormone and stimulated by larger doses (212). In fasted rabbits large doses produced a prolonged hypoglycaemia and small doses an immediate hyperglycaemia. These various observations suggest the possibilities that the insulin-like action of growth hormone may be attributable to the pituitary growth hormone itself, or a particular fraction thereof, or to a new substance associated with it, or to bound inactive insulin liberated from the tissues by the growth hormone.

Insulin and protein metabolism.—Evidence indicating that insulin promotes protein anabolism continues to accumulate. The classic work of Mirsky and his associates which showed that in nephrectomized dogs and eviscerated dogs insulin suppressed urea formation and accelerated the utilization of amino acids again has been confirmed (213). Insulin promotes growth and protein synthesis in the hypophysectomized rat (214, 215). There is some controversy as to whether these effects of insulin are direct or the result of increased caloric intake. However, as a rule an increased caloric intake in the insulin-free animal does not increase nitrogen retention.

The results of *in vitro* investigations are in accord with those obtained *in vivo*. Insulin added to the rat diaphragm *in vitro* stimulated the incorporation of labelled amino acids into the protein of this tissue (216, 217). Krahl (217) observed that the amino acid uptake by isolated diaphragm and liver slices from diabetic rats was markedly reduced. Lukens reviewed the subject of insulin and protein synthesis and agrees that insulin undoubtedly restores

protein synthesis to normal in diabetic tissues but he contends that evidence indicating that this hormone can cause protein to be synthesized at a greater than normal rate, is equivocal (218, 219). The protein anabolic effect of testosterone apparently is obtained only if insulin is available (220).

Insulin and fat metabolism.—Several laboratories have been active in studying the role of insulin in promoting fat synthesis from glucose, fructose, lactate, acetate, acetoacetate, and octanoate in eviscerated animals, mammary gland slices, and liver slices from normal, diabetic, and Houssay animals. Reviews of certain aspects of this work are available (91, 97, 109, 221).

The alpha cells of the islets.—The physiology and morphology of the α cells of the pancreas have been reviewed recently (5, 222, 223, 224). The views expressed differ somewhat. The specific destruction of the α cells by cobalt chloride is discussed in these reviews. Small repeated doses of cobalt chloride were stated to result in an increase in α cells (8). Synthalin A (decamethylene diguanidine) was reported to cause gross hydropic degeneration of the α cells of the rabbit pancreas (225). Sodium diethyldithiocarbamate caused islet changes in rabbits but, contrary to the earlier report of Kadota and Midorikawa, specific necrosis of α cells was not seen (225).

Mayer (226) postulated that the hereditary obese-hyperglycaemic syndrome in mice is associated with hypersecretion of the α cells of the islets and that the α cell-secretion is controlled by growth hormone. The α cells have been considered by some to be the site of origin of glucagon. Such a large volume of literature on glucagon has appeared that this part of the subject merits separate consideration.

Glucagon, the Hyperglycaemic Factor of the Pancreas

From 1923 to 1948 the term "glucagon" was used almost exclusively in the predominantly German literature to name and describe the action of the hyperglycaemic material found together with insulin in extracts of the pancreas. In the period between 1948 and 1952, the term "hyperglycaemic-glycogenolytic factor (HGF)" was similarly employed in about 80 per cent of publications relating to this material. Since 1952, the term "glucagon" is again being used in most publications on the subject and will be adopted in this review.

Site or sites of origin of glucagon.—Glucagon has been extracted from the pancreas and in some species, from the gastrointestinal mucosa, but not from other tissues of mammals (223). From indirect evidence, it has been proposed that pancreatic glucagon originates in the silver-staining α cells of the islets of Langerhans and in cells with similar staining reactions in the gastrointestinal tract (223). This hypothesis has been supported (5, 224, 226 to 229) and all or parts of it challenged (64, 222, 230). Davis recently observed that in the rabbit no cells of the gastric mucosa have all the staining properties of the α cells, and hence none of the gastric mucosal cells can be considered as similar to α cells (231). Active glucagon has been found to be higher in concentration in blood from the pancreatic vein than from peripheral

veins (37, 232). Thus the inference that the intact pancreas releases glucagon under an adequate stimulus has received some direct support.

Extraction and assay of glucagon.—Most widely used in the extraction of pancreatic glucagon is the ethyl alcohol-HCl procedure for extracting insulin (233). The extraction of glucagon with warm water, followed by isoelectric precipitation (234), and its extraction by liquid ammonia (232) have been reported. Crystalline glucagon has been recovered by further fractional isoelectric precipitation from an amorphous fraction obtained during the purification of commercial insulin (235).

Most early estimations of the potency of glucagon preparations were based on the extent of the initial elevations in blood sugar levels following their injection into test animals, or by the glycogenolytic action of such preparations on liver slices. The rabbit liver slice is claimed to be eight times as sensitive as the rat liver slice for glucagon assay (236). In a variant of the liver slice method, excised liver was perfused with a glucagon-Tyrode solution, the increase in glucose in the perfusate being measured (237). The cat is reported to be more sensitive than the rabbit to intravenous glucagon, and 0.1 μg. of crystalline glucagon administered to the cat has been proposed as a standard for glucagon assay (235). Designs of single and of multiple dose methods for the assay of glucagon have been proposed (227). Cross-circulation (232) and blood transfer (238) have been used only as semi-quantitative methods for glucagon detection in the blood.

Chemical nature and properties.—Crystalline glucagon (235, 239) and, independently, a purified amorphous glucagon (234) were found to be protein in nature, and sharply differentiated from crystalline insulin in amino acid composition. On this basis, it has been concluded that glucagon could not represent a degradation product of the established hormone, insulin. Neither of the above glucagon-concentrates contained appreciable cystine or zinc, both of which substances are important constituents of crystalline insulin. Other workers have reported zinc to be present in all glucagon preparations tested. An increase or the complete removal of organically bound zinc from such glucagon preparations was accompanied respectively by an increase or the complete loss of their hyperglycaemic potencies. The magnitude of the initial hyperglycaemia following the injection of solutions of crystalline insulin preparations also was found to vary directly with the content of zinc in such insulin crystals, falling to zero when the zinc content was below 0.5 per cent (240). The conflict of these results with those mentioned above may be attributable to the presence of certain zinc-alpha-amino acid complexes in the glucagon preparations. Many such complexes have been found to be effective in producing a transient hyperglycaemia following their intravenous injection in rabbits though the amount of zinc injected was less than 1 μg. (241).

The glycogenolytic action of glucagon on liver slices is associated with a rapid increase in the concentration of active phosphorylase, probably the result of its formation from inactive phosphorylase in the intact liver cells.

The increase in active muscle phosphorylase observed to follow the action of epinephrine was not noted with glucagon (242). The adrenergic-blocking drug, dihydroergotamine, prevents the hyperglycaemic action of epinephrine but not that of glucagon on liver cells, indicating that some as yet unspecified difference exists in the means whereby these two agents act on the liver phosphorylase enzyme system (243).

The effect of the injection route.—The hyperglycaemic action is reported to be greatest when purified glucagon is injected intraportally, that is, by its physiological pathway into the liver. Less effective in the order shown are intravenous (peripheral vein), intraperitoneal, intramuscular, and subcutaneous methods of injection (224, 244, 245). The finding by others that intravenous and subcutaneous injection routes are equally effective (246) emphasizes the caution which must be employed at this time in making generalizations concerning the properties and effects of unpurified extracts of pancreas described as glucagon.

Factors influencing glucagon release from the pancreas.—From cross-circulation experiments with dogs, it appeared that glucagon was released into the portal blood when the blood sugar concentration was subnormal, insulin being released when it was above normal (232). However, the glucagon extractable from the pancreas in normal and insulin resistant mice was found to be significantly elevated after a truly massive dose of insulin (247). The administration of pituitary growth hormone augmented the release of glucagon into the portal blood (37, 232). Glucagon was found in the perfusate from excised pancreas when the concentration of sugar in the perfusing fluid was subnormal (237), indicating that the pituitary factor is probably not essential for glucagon release.

Sites of action and effects.—The vascular juxtaposition of pancreas and liver, the increased hyperglycaemic activity of glucagon introduced into the portal vein, and the observation that its activity but not that of insulin was removed on perfusion through isolated frog liver (248) indicated that the liver may be the chief organ directly affected by glucagon released under physiological conditions. Breakdown of liver glycogen to dextrose is still the outstanding primary effect claimed for glucagon (244, 249, 250, 251). Effects resulting from the injection of glucagon such as the increase in liver fat (252, 253), in urinary nitrogen excretion (254), or in muscle glycogen (250) may be secondary to the breakdown of liver glycogen. On the other hand, the administration of glucagon to the eviscerated-nephrectomized rabbit has been shown to decrease the rate of transfer of glucose from the extracellular to the intracellular body space. In this regard its action is found to be antagonistic to that of insulin (255). The claim that glucagon promotes somatic growth in rats (256) has found no support in subsequent experiments (257).

Glucagon and pathological conditions.—Much indirect evidence and speculation that glucagon may initiate diabetes mellitus or influence its severity has been presented and reviewed (5, 37, 226, 244, 258). More recently several

direct attempts at producing a diabetic state in animals with glucagon have been published. Intact force-fed cortisone-treated rats given glucagon showed hyperglycaemia and glycosuria but only for the duration of the treatment (224). Glucagon without the cortisone did not produce diabetes. On the other hand, ACTH but not cortisone enhanced the hyperglycaemic action of glucagon in rabbits (259). Intravenous but not subcutaneous glucagon administered to partially depancreatized rats caused only a temporary excacerbation of the diabetes (260).

In human subjects, the transfer of whole blood from diabetic donors to nondiabetic recipients caused a rise in the fasting blood sugar level in 32 per cent of the patients studied, leading the observer to subclassify the donors as glucagon-hyperglycaemic diabetic subjects (238), though this seems to be unjustified until the substance producing the hyperglycaemia is more specifically established. The hour-long intravenous injection of purified glucagon into fasting human subjects with stable and unstable diabetes but not receiving insulin, resulted in a greater and more prolonged transient rise in blood sugar in the former than in the characteristically young unstable subjects (261). Similar findings, but reversed for the two types of diabetes, had been reported earlier in fed diabetic subjects receiving insulin (244).

From the above evidence there is little doubt that the injection of glucagon intensifies existing diabetes. The evidence that it may be diabetogenic in the intact animal is not definite. It may be that the administration of this fleetingly active agent continuously into the portal circulation will produce more definite effects.

The possibility that liver glycogen storage disease may represent the result of an insufficiency of glucagon secretion has, on the whole, received little support from the results of the administration of glucagon (244, 262). Clinical evidence has been presented that some cases of spontaneous hypoglycaemia in children are associated with the absence of α cells in the islets of Langerhans (263).

The summing up.—Since Minkowski and von Mering showed the relationship of the pancreas to diabetes mellitus there has been a great deal of research on the effects of the pancreas on metabolism. This field, far from being exhausted, has become increasingly productive, as the reports of the last two years clearly show. The discovery of insulin stimulated a new series of studies on the relation of the endocrine pancreas to carbohydrate metabolism, to fat metabolism, and, more recently, to protein metabolism and growth. Factors influencing the insulin-producing structures have received attention also, and the hyperglycaemic effect of insulin preparations has developed from an interesting side-effect into a whole new field of investigation. Indeed, the possibility that there is a second pancreatic hormone, though still challenged, is receiving increasing support. None of these major lines of investigation was initiated during the period reviewed, but many new approaches have been noted and our understanding of these problems has been enhanced.

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THYROID[1,2]

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Without wasting any more of the few precious pages allotted to this once-in-three-years survey of thyroid biochemistry and physiology than necessary to point out its major shortcoming, the author wishes to emphasize that omission of a publication here has no absolute implication of inadequacy. Moreover, one entire phase of recent thyroid development has been omitted *in toto*: the fascinating one of specific plasma protein transport of thyroxine as the major circulating thyroid hormone, a development which blunts the edge of Albert's critical remarks anent "protein-bound iodine" in the last *Annual Review*, of 1952 (3). This was done, again, because of space limitations, and because the present author drew up a section of the 1954 Brookhaven Conference on the Thyroid devoted to this subject (17). Although the formal publication from this conference has not appeared so soon as six weeks afterwards, it is promised for a date well in advance of the 1954 *Annual Review* volume, and interested readers are hereby referred to it. Another note of explanation may also be offered: the general tone of this review will be one of critical examination of experimental work. No clinical material is even summarized, despite the clear and impelling value of this line of work, unless it has physiological bearing.

Several other reviews of various phases of thyroid work, some excellent, have appeared in the past three years, and these can be recommended without more than brief mention of the particular aspects dealt with. Lardy & Feldott (133) presented their investigation of the *in vitro* effects of thyroxine in detail. Much of the energy metabolism work prior to 1951 was summarized by Barker (16). Roche & Michel (178) discussed iodoproteins. Riggs (172) surveyed the quantitative aspects of iodine metabolism and Gross & Pitt-Rivers (98) the experimental usefulness of radioiodine. The history of triiodothyronine was told by Thibault (208). McCullagh (150) examined critically the theories offered in explanation of the exophthalmos of Graves' disease, and Thompson (211) discussed changing concepts in thyroid physiology and therapy. Rawson's talk before the Federation summarizing some very recent thyroid advances has appeared (169).

The Thyroid Gland

Embryonic development.—Reports of iodine metabolism of the chick embryo disagreed somewhat as to the day thyroid function started, with Trun-

[1] The survey of literature pertaining to this review was completed in July, 1954.

[2] Much as the present author dislikes abbreviations as substitutes for words, he has been forced by the exigency of limited space to employ many. He hopes that all readers will themselves put in the entire word for the following: ACTH (adrenocorticotrophin); BDHB (*n*-butyl-3,5, diiodo-4-hydroxybenzoate); PBI (protein-bound iodine); PTU (propylthiouracil); T:S ratio (thyroid to serum ratio); TSH (thyroid-stimulating hormone); TRIT (triiodothryonine).

nell & Brayer (214) placing I^{131}-concentration by the thyroid at the end of the tenth day of incubation. TSH[3] did not shorten the time at which I^{131} uptake started, but did increase the amount. Wollman & Zwilling (241) injected I^{131} into an allantoic vein of seven- and nine-day embryos and found a four- to seven hundredfold concentration of activity in the thyroid compared with that in serum (T:S ratio), almost all nonprecipitable (that is, "inorganic"). At nine days, the T:S ratio was about 5,000, and the iodide was mostly in protein-bound form. Hunt (119) also injected chick embryos with I^{131} at seven days, but was not able to detect uptake until the ninth day, after which the level rose, with spurts on the fourteenth and fifteenth days and at hatching. Radioautography showed the thyroid and the pigmented layer of the eye to be the only areas of concentration of activity.

In Vidal's sections of developing chick embryo thyroid, colloid droplets first appeared at 11 days and progressed to follicles by 15 days (225). When thyroxine was injected into the vitellin sac at seven days, development was delayed and the gland weight was 40 to 50 per cent of normal. Rondon-Tarchetti (180) noted colloid droplets and follicle formation first showing up at 16 days. When thyroid explants from 15-day embryos were grown in embryo extract-plasma clots, colloid and follicle development were seen during the next 48 hours, corresponding to the rate of differentiation *in vivo*.

Twenty-four hours following intravenous injection of I^{131} into pregnant, near-term cows, Gorbman *et al.* (92) found slightly more activity in the fetal than in the maternal serum; in both the active fraction was primarily inorganic iodine with a small amount of thyroxine. The fetal thyroids contained a total of about twice as much I^{131} as did the maternal, with a six- or sevenfold greater concentration. One-fifth of the organic I^{131} had been incorporated into thyroxine by the fetal gland at a time when only a trace was present as thyroxine in the adult, probably attributable to differences in TSH secretion.

Lower vertebrate forms.—The taxonomic interests of Gorbman have resulted in reports of widely varying thyroid activity in various fish, from the shark (93) showing a rapid uptake of I^{131}, synthesis going through monoiodotyrosine and diiodotyrosine to thyroxine, to the domesticated goldfish (26) showing a peak of only 3 per cent uptake. Synthesis in this form proceeded only as far as diiodotyrosine, since no thyroxine was found present. When TSH was injected into the goldfish, I^{131} uptake and turnover was considerably increased and small amounts of thyroxine were found. Such findings may have a bearing on deciding which steps of thyroxine synthesis are not enzymic; if the diiodotyrosine to thyroxine transformation is not enzyme-catalyzed, why should it be interrupted in any thyroid capable of forming diiodotyrosine itself? The platyfish displayed a 30 per cent uptake at 24 hr. coupled with a slow discharge (25). Thyroxine did not appear until 48 hr., but finally reached a maximum of 15 per cent of the thyroidal I^{131}. The marine lamprey, claimed to have no thyroid, has been found to accumulate I^{131} in the form of colloid in elongate but otherwise typical follicles located in the pharyngeal floor (91).

Microscopic anatomy and intracellular activity.—Two laboratories using

electron microscopy have reported structural items of great interest in the thyroid acinar cells: a brush border towards the colloid, and strands or canaliculae in the cytoplasm. Monroe (153) called attention to the similarity between absorptive functions and brush borders in other tissues. Braunsteiner Fellinger & Pakesch (35) observed changes in the filamentous projections suggestive of secretion into the colloid early after TSH injection into the donor animals, followed by elongation of filaments, projection of follicular cells into the lumen, and colloid depletion, all indicative of resorption of colloid. The strands of material considered by Braunsteiner *et al.* as ribonucleic acid-protein were described by Monroe as usually aligned parallel to each other in the cytoplasm and appearing as tubules in some fixatives.

Visualization of I^{131}-incorporation into colloid by radioautography has been carried out many times, but Leblond & Gross (136) were able to show activity clearly in the cells before the colloid. Sufficient activity could not be introduced into the cells to enable early intracellular localization. Nadler, Leblond & Bogoroch (156) have more recently quantitated the rates of accumulation and discharge of I^{131} and pointed out that the biological half-life of iodine in the follicular colloid increased with the size of the follicle. Clayton (48) also demonstrated a high I^{131} concentration in small follicles as well as an uneven distribution within the larger.

Pitt-Rivers & Trotter (166) found that propylthiouracil-blocked rat thyroids still secreted I^{131} into the colloid, even though chromatography of gland extracts showed that only inorganic iodide was present. They found no localized radioactivity in salivary glands, probably because the I^{131} was not stored but passed into the saliva as rapidly as it was removed from the plasma. Radioautography obviously cannot reveal the intimate nature of the material comprising radioactive colloid.

Histochemical studies on ditetrazolium chloride reduction by intracellular thyroid succinic dehydrogenase revealed activity first appearing at the interfaces of neutral red-staining vacuoles, where dictyosomes and mitochondria are located, then extending to the entire mitochondrial apparatus (85). Some cells even developed pigment in undifferentiated cytoplasm. Rerabek (171) found only half of the desoxyribonucleic acid in the nuclear fraction of thyroid cell homogenates, with the rest of it, 87 per cent of the ribonucleic acid, and 95 to 97 per cent of the diiodotyrosine and thyroxine in the supernate from the microsomes. This cannot be interpreted as specific localization of thyroxine or diiodotyrosine in the supernate, since no attempt was apparently made to remove colloid before fractionation.

Pitney & Fraser (165) have made use of milk xanthine oxidase to set up an artificial protein iodination system, separable into an enzymic and a nonenzymic portion, the latter duplicable by the outside addition of hydrogen peroxide:

(*a*) Enzymic: Xanthine + O_2 + oxidase → H_2O_2 (+ uric acid)

(*b*) Nonenzymic: H_2O_2 + NaI → I°(+ H_2O + Na_2O) + Casein → Iodocasein

When tested with the complete system, thiouracil, 2-carbethoxythio-methyl-

glyoxaline (Neo-Mercazole), and, surprisingly, potassium thiocyanate showed a very rapid 90 per cent inhibition; resorcinol and sulfathiazole produced a more gradually increasing inhibition with increasing concentrations. With resorcinol at $10^{-6}M$, inhibition of the enzyme reaction was 90 per cent, of the nonenzymic reaction 35 per cent, but thiouracil under the conditions used was unable to compete with casein for iodine. This test system is deserving of a much more detailed analysis to determine possible relationship to the thyroid system, especially since Pihar (164) has shown methylthiouracil capable of inhibiting the thyroid gland xanthine oxidase.

In a series on the *in vitro* metabolic activity of beef thyroid tissue, Weiss (227) noted the disappearance of lactate and the lack of effect of added TSH or thyroxine on the Q_{O_2} of slices. Radioiodide was incorporated into diiodotyrosine and thyroxine by slices, but not by homogenates until copper ions and tyrosine were added (228). Fawcett & Kirkwood (66) challenged Weiss' homogenate findings on the basis of their evidence for enzymatic formation of 3-monoiodotyrosine by thyroid homogenates. They demonstrated this compound chromatographically and claimed that the usual type of butanol extraction procedure allowed monoiodotyrosine to appear in both "diiodotyrosine" and "thyroxine" fractions. It is generally agreed that some sort of oxidase in the thyroid gland transforms iodide into a more reactive form. A tremendous body of literature deals with the nonenzymic formation of iodoamino acids when tyrosine, free or in a protein, is reacted with iodine, but it is not yet possible to decide whether thyroidal synthesis is nonenzymic over the same series of compounds. The demonstration of enzymic iodination of tyrosine even to the monoiodinated form is an important observation.

Because thyroxine is produced in protein combination but is liberated in free form, proteolysis of the colloid must occur (DeRobertis). Gordon *et al.* (94), and McQuillan & Trikojus (151) prepared thyroid protease nearly free of thyroglobulin and showed a pH optimum of 2.5 to 3.5, no activation by TSH, thioglycollic acid, cysteine, Mn^{++}, Ca^{++} or trypsin. No free thyroxine was found, a process possibly requiring a peptidase. Weiss (229) has recently delineated the ion activation and inhibition spectrum for thyroid proteinase and peptidase activity. He also found a low pH optimum (4.0) for proteinase, with very little activity remaining at the colloid pH of 6.6. Although the proteinase was found in all subcellular fractions, it was highest in the nuclei and mitochondria.

Working with alkaline phosphatase of thyroid glands of hypophysectomized rats, Fels, Simpson & Evans (68) observed a marked Mg and Mn stimulation which was absent in normal glands. Injection of TSH eliminated the Mg effect and the authors suggested that hormonal control of glandular activity might be exerted through metallic activators.

General aspects of function, iodine-trapping.—Albert (3) pointed out the triplex nature of thyroid gland function: trapping of iodide, synthesis of organic iodine, and secretion of hormone. Methods for the study of each of these have been proposed, but have not been fully evaluated and, themselves,

often involve drastic alterations in thyroid operations. For example, in studying iodide uptake by the thyroid, it is almost routine to block organic synthesis with a thiouracil, despite many demonstrations that goitrogens greatly increase the size of the thyroid "iodine trap," measured in terms of the ratio of thyroidal I^{131} to serum I^{131}. Thiouracil also sensitizes the gland to TSH.

Because of the complicated nature of thyroidal metabolism of iodide, simple measurement of uptake of I^{131} can no longer be considered an adequate analysis. As pointed out by Wollman & Scow (240), if organic incorporation of iodide was allowed to proceed, even at two hours 97 per cent of the gland activity was held as organic I^{131} in the mouse. Although the figures for rats may be less, fractionation of total thyroid iodine is more reliable than assuming the 4-hour uptake to be bound inorganic and the 24-hour organic.

Although it is well-established that the second stage of synthesis of organic iodine from iodide proceeds through the steps of monoiodotyrosine, diiodotyrosine, to thyroxine, the role of triiodothyronine as an intermediate, stressed by Roche *et al.* (177), or as a product of deiodination of thyroxine as proposed by Gross & Pitt-Rivers (101), has not been fully evaluated. The participation of enzymes in the activation of iodide and probably in some parts of the organic syntheses has already been mentioned.

To study the final stage of secretion of thyroid hormone, administration of I^{131} a sufficiently long time (usually a matter of days) before the experiment ensures its nearly complete incorporation into organic form as well as elimination of inorganic I^{131} from the body (6). Activity then represents discharge, or secretion, of hormone. Reincorporation of I^{131} liberated by deiodination can be prevented by blockade with I^{127} or other agents. Studies to date have often overlooked the complicated events taking place in the thyroid. As an example, Botkin & Tew (33) found that epinephrine produced a decrease from control quantities of thyroid I^{131}, which they interpreted as an increased discharge of hormone, despite the facts that this was a four-hour uptake and that no differentiation was made of the I^{131} into inorganic and organic.

Halmi (107) noted that a low-iodine diet, even in the absence of the pituitary, expanded the ability of the thyroid to trap iodide, often without morphological change in the gland. Corrected for "iodide space" in the thyroid gland, values for maximal thyroid iodide uptake were obtained for the following states: 3 mg. I/100 gm. in hypophysectomized, 20 in normal, 41 in TSH-injected hypophysectomized, 80 in propylthiouracil-injected normals. Thus, at one extreme of iodine deficiency, iodine lack itself seemed to predominate in activation of the trapping mechanism, while at higher levels of iodide intake the influence of TSH on the gland became of greater importance.

Since even in the presence of constant doses of TSH, the thyroid uptake was inversely related to its own content of iodide, primarily organic, Vanderlaan & Caplan (218) theorized that iodide uptake of the gland may be a purely intrinsically controlled process, not directly dependent upon TSH. Pitui-

tary secretion of TSH would then be sensitive to the circulating level of thyroid hormone. Such a concept would explain the high T:S ratio[2] in thyrotoxicosis on the basis of the lowered stores of organic iodine rather than an increased TSH (actually not found). This still does not give any hint as to the nature of the stimulus causing the thyroid to initiate and to maintain a high rate of secretion of hormone.

Money, Rall & Rawson (152) placed rats on an iodine-deficient diet and detected an increased uptake of I^{131} by 10 days, the time at which the I^{127} content of the gland started down. There was no change in gland size for 106 days, at which time the serum protein-bound iodine (PBI) began to fall. An inverse relationship between current iodide availability to the gland and its uptake of iodide was also observed by Fish, Carlin & Hickey (70). The rapidity of establishment of equilibrium between thyroid and plasma iodide pool was further illustrated by Storaasli *et al.* (203), who demonstrated an increase in I^{131} uptake from 18 per cent to 51 per cent merely by withholding food and water from the animals during the 24 hours following administration of the isotope.

Wollman & Scow (239) found that hypophysectomizing normal or thiouracil-treated mice caused a progressive decrease in T:S ratio and in I^{131} uptake as well as in conversion to thyroxine. Albert, Tenney & Lorenz (8) found renal I^{131} clearance of hypophysectomized rats lowered to 10 to 25 per cent of normal, whereas thyroidectomy had no effect. They pointed out that the lowered thyroid uptake in hypophysectomized animals occurs in the face of increased availability of iodide. In patients with various types of kidney disease, Perry & Hughes (162) encountered lowered renal clearance of iodide. When I^{131} was used to follow iodide disposal, a lowered thyroid uptake was found despite the elevated plasma I^{131}. The explanation was revealed when chronic I^{127} retention was demonstrated; since the patients' thyroids had been saturated at high levels of iodide, uptake was depressed. However, the 26-hr. values were essentially normal.

Discharge of iodide trapped by the thyroid but not yet synthesized into organic form was rapidly effected by perchlorate, and this ion was also found by Wyngaarden, Stanbury & Rapp (243) to interfere most effectively with the iodide-concentrating capacity of the thyroid, leading, in that order, iodide, thiocyanate, and nitrate. Some sort of competetive process was indicated by the fact that iodide would overcome the effect of perchlorate and thiocyanate, although it is known that the latter is not significantly concentrated from the plasma by the thyroid.

Pituitary-thyroid relationship.—Halmi *et al.* (110) showed that hypophysectomy lowered the T:S ratio to 6 from the normal of 25, but that prolonged thyroxine injection would drop it still lower, to 1. The dual nature of the thyroxine effect was further demonstrated by its ability to depress iodine trapping of the hypophysectomized rat. Injection of even a single dose of TSH elevated the T:S ratio after a latent period of 5 to 6 hr. If PTU[3] was injected together with the TSH, the effect was enhanced, but thyroxine did not alter the response to TSH.

Greer (96, 97) noted that interrupting the normal contact of the pituitary with the hypothalamus by electrolytic lesions or by hypophysectomy combined with intraocular transplants interfered with growth stimulation of the thyroid cells in response to PTU, but did not prevent the usual PTU-induced tenfold increase in T:S ratio. This was interpreted as the secretion of two TSH factors, one regulating thyroid growth, and one thyroid metabolism. Bogdanove & Halmi (31) confirmed Greer's basic observations, but considered the changes as being attributable to a quantitative rather than a qualitative difference in TSH secretion. Probably the most telling argument was the finding that PTU combined with TSH injections in hypophysectomized rats greatly potentiated the T:S ratio raising effect of TSH even though the quantities given were not sufficient to restore the normal morphological picture of the thyroid. Further support was furnished by Goldberg, Greep & Nay (86), who found that maintaining hypophysectomized rats on a low-iodine diet increased thyroid I^{131} uptake compared with controls on adequate amounts of iodine, although there was no change in gland weight and only slight increase in cell height.

Stalk section in rats, according to Barrnett & Greep (21), produced less thyroid, adrenal, and gonad atrophy than hypophysectomy. The responses to cold exposure and thiouracil feeding were still present, although much diminished. Release of pituitary TSH and ACTH seemed to depend upon the circulating levels of the peripheral hormones and not upon direct neural or neurovascular connections with the hypothalamus. The quantitative difference may be a result of interference with blood supply.

Halmi (105) and Purves & Griesbach (167) have independently proposed cytologic differentiations of two basophils in the rat pituitary, one for TSH and one for gonadotrophin. As rationalized by Halmi, agreement is good, despite some differences in terminology.

Fels and co-workers (69) continued the discussion, started with ACTH, of pituitary trophins as small molecular size substances, by reporting the papain digestion of purified TSH to active material dialyzable and nonprecipitable by trichloroacetic acid. This claim has not aroused as much controversy as that of Dobyns & Steelman (58), that TSH activity could be separated from exophthalmos-producing substance. This would be an attractive explanation for the many clinical discrepancies regarding exophthalmos. Simkin & Starr (193) have reported failure to produce exophthalmos in euthyroid, pituitary hypothyroid, or athyreotic humans by injections of TSH for periods up to 22 days. When the thyroid was present, Williams (237) found cortisone injections produced exophthalmos in young adult guinea pigs, rabbits, and rats; Aterman & Greenberg (13) produced the same effect in immature rats.

Inhibition of thyroid gland function by thyroid hormone itself still is a challenge. Perlmutter *et al.* (160) were able to reduce thyroid I^{131} uptake to hypothyroid levels with a daily intake of desiccated thyroid inadequate to elevate the PBI^2, and producing only a slight increase in BMR. Under these conditions, TSH injection still produced a marked effect on the thyroid gland

metabolism, so the desiccated thyroid inhibition could not have been on the thyroid, but on the pituitary release of TSH. Starr & Liebold-Schueck (202) found an even more striking effect with triiodothyronine. On the other hand, Shellabarger & Godwin (190) obtained evidence in the chick that thyroxine and triiodothyronine could depress the effect of exogenous TSH on thyroid weight, but not on I^{131} uptake.

Werner, Hamilton & Nemeth (230) reported that desiccated thyroid did not depress the hyperactive thyroid in Graves' disease, but the gland would still respond to TSH injection. The driving stimulus to the thyroid thus arises outside of the pituitary. After successful I^{131} therapy, pituitary control tended to be re-established. Zondek (247) objected to discarding the pituitary as the cause of hyperthyroidism.

When I^{131} was injected into rabbits, the thyroid was the first to show activity, followed 4 to 7 hr. later by the posterior pituitary which, at the latter time, had the highest activity next to the thyroid. Since neurohypophyseal I^{131} was no higher than other tissues in the absence of the thyroid, Jentzer (123) concluded that it represented a specific thyroxine-concentrating function. Jensen & Clark (122) also demonstrated localization of radioactive thyroxine in the neurohypophysis.

Adrenal cortex and other endocrines.—The dissension in the literature concerning cortisone as an inhibitor of thyroid function appears to have been largely attributable to differences in what function was being measured. There is no doubt of a decrease in I^{131} uptake, which is almost certainly attributable to the increased iodide excretion caused by the steroid (120), leaving a lowered plasma I^{131} level available for thyroid uptake. Such an indirect effect explains most experiments with cortisone, such as the depression of TSH-maintained I^{131} uptake of hypophysectomized rats reported by Verzár & Vidovic (223). However, Perry (161) supported cortisone interference with thyroid I^{131} uptake without alteration of hormone release, and Zingg & Perry (246) even demonstrated lowered thyroid uptake and clearance of I^{131} in human subjects receiving desoxycorticosterone acetate (DCA), cortisone, or progesterone, in the absence of any renal changes. Although the data of Boatman *et al.* (29) show little effect of DCA, the authors concluded that the uptake was increased.

The thyroid iodide trap was not directly altered by cortisone, and there was actually a slight enhancement of thyroid cellular hypertrophy from injected TSH in hypophysectomized rats or from PTU in normal rats (106, 109). D'Angelo and co-workers (53) noted cortisone potentiation of the goitrogenic effect of PTU on rats, which they interpreted as resulting from increased pituitary action. Gabrilove, Dorrance & Soffer (77) found that corticotrophin injections prevented some of the thyroid hypertrophy seen in rats on a PTU-containing diet. Neither cortisone nor desoxycorticosterone had any effect, and the authors concluded that ACTH must at least partially inhibit TSH release.

Albert, Tenney & Ford (7) found no interference by ACTH or cortisone with the discharge of bound I^{131} from the thyroid and, with a larger dose of

cortisone, Halmi & Barker (108) obtained lowered thyroid PBI and raised plasma PBI. On the contrary, Brown-Grant and co-workers (40) claimed epinephrine, ACTH, and cortisone all inhibited thyroid iodine release in the rabbit. Flückiger and Verzár (72) reported decreased I^{131}-uptake and release following epinephrine injections.

Cortisone did not alter the response of hypophysectomized dogs to single or repeated injections of TSH, according to O'Neal & Heinbecker (157). No alteration of thyroid weights or histology in dogs or rats was seen after protracted periods of cortisone injection, with unchanged (or slightly elevated) plasma PBI and no interference with propylthiouracil goitrogenic action. Kuusisto & Telkkä (132) found no effect of cortisone added to aquarium water on the metamorphosis of tadpoles or the histology of their thyroids.

When euthryoid patients were given very large doses of estrogens (usually diethylstilbestrol) by Engstrom & Markardt (63), the serum PBI increased during three to four weeks, and leveled off about 2 μg. per cent above the start values. In contrast, Tuchmann-Duplessis & Mercier-Parot (215) found a slight depression of thyroid cell height in male rats castrated or estrogen-injected. Siegel & D'Angelo (192) had previously shown that the thyroidal depression following castration was attributable to decreased circulating TSH. Hess (113) found the most marked organ changes after thyroidectomy of adult rats to appear as testicular and seminal vesicle hypertrophy which he attributed to an increased sensitivity to pituitary gonadotrophins.

Effects of cold and other types of stress on thyroid.—Catz, Rawi & Geiger (42) found thyroid I^{131}-uptake increased in cold-exposed rats tested at one, two, and four hours. At 24 hours cold-exposed and controls were the same, indicating increased formation, release, and utilization of thyroxine. Verzár, Vidovic & Hajdukovic (224) produced actual hypothermia in rats by a combination of chilling and anoxia and were able to arrest thyroid activity completely for 8 hr. at a body temperature of 15° to 20°C. As rewarming was allowed, thyroid function returned. Even repeated bouts of hypothermia produced little permanent alteration of thyroid function. Reduced atmospheric pressure depressed thyroid function as well as body temperature with the former returning to normal more rapidly. A nice contrast in reaction of the rat (nonhibernator) and hamster (hibernator) to low temperature was obtained by Deane & Lyman (54). The hamster lost weight, the adrenals decreased in size and the thyroid was little changed as the animal was depressed, in contrast to the stimulation of adrenals and thyroids of the rat.

There was a very slightly increased thyroid synthesis of organic iodine during the first day after whole-body irradiation, followed by a depression to 33 per cent of normal at four days (32). Van Middlesworth & Berry (222) reported a decreased 24 hr. I^{131} uptake and plasma PBI^{131} resulting from a variety of stress situations: anoxia, nephrectomy, surgical trauma, starvation, and deficiencies of Vitamins A, B_1, B_2, B_6. These animals were on a low-iodide diet before the start; in contrast, Catz, Rawi & Geiger (41) showed that starvation during the 24 hours elapsing after I^{131} injection doubled the uptake. This was probably a result of the iodide deprivation, short as it was,

because replacement of the missing calories during the fast with glucose did not decrease the fasting elevation.

When rats were given only 25 per cent of the control amount of calories but with protein intakes either 25 per cent or 100 per cent of the controls, weight loss of thyroid and adrenals was less dependent upon protein lack than was weight loss of the ovaries, testes, uterus, seminal vesicles, and kidneys (173).

Thyroid gland inhibitors.—When substitution was made on the S of 2-mercapto-1-methylglyoxaline or dimethylthiohydantoins, antithyroid activity was retained only if the group could be removed in the body (45). For instance, 2-carbethoxythio-1-methylglyoxaline was as active as the parent compound; in fact it is being used clinically. The benzylthio compound, however, was only one-tenth as active. Lawson & Searle (135) have been able to iodinate some of these substituted thioglyoxalines and believe their antithyroid activity is exerted in this manner. Fawcett & Kirkwood (65) have equated aromatic thyroid-inhibiting compounds with their possession of electron-donating groups, enabling formation of molecular addition compounds with I^0, rearranging to become stable iodine-substituted compounds when bond energies were sufficiently high, as with resorcinol and phloroglucinol. On the other hand, Arnott & Doniach (11) and Rosenberg (181) considered a series of compounds related to resorcinol as specific inhibitors of thyroid peroxidase on the basis of their depression of the milk peroxidase discussed earlier. Fawcett & Kirkwood (65), presenting chromatographic evidence for iodoresorcinol and iodophloroglucinol formation in thyroids inhibited by these two aromatic compounds, concluded that peroxidase activity could not have been seriously impaired. It is clear that much more information is needed concerning the enzymatic basis of thyroid function, especially the differentiation from nonenzymatic reactions.

The developing chick embryo has been employed by Adams & Buss (1) to compare the effects of several goitrogenic agents on the developing thyroid. After a single injection of thiourea, methylthiouracil or propylthiouracil on the fourteenth day of incubation, histological changes of colloid loss, increased cell height, and increased number of mitoses were noticed within 24 hours. Thyroid weight increased. These changes continued to increase to a variable extent but remained high through the rest of the incubation period. Amphenone B [1,2-bis-(*p*-aminophenyl)-2-methyl-1-propanone dihydrochloride] tested in this manner proved goitrogenic.

Searle, Lawson & Morley (188) have tested the antithyroid properties of a considerable number of mercaptoglyoxalines, mercaptothiazoles, and thiohydantoins. Despite continuing clinical opinion favoring iodothiouracil as having unique thyroid-depressing properties (43), a barrage of reports indicates that this is without solid experimental basis (4, 88, 219).

It still is not clear how certain anions (perchlorate, thiocyanate, nitrate) act to displace inorganic iodine from the thyroid trap, but Wyngaarden, Wright & Ways (244) pointed out that inclusion of perchlorate, the most po-

tent of this group, in the drinking water of rats caused the typical signs of thyroid inhibition.

Plant biochemists have been challenged by the possibility of antagonism between thiouracil and uracil. Jeener (121) showed that thiouracil could be incorporated biologically into the ribonueleic acid of tobacco mosaic virus, and that the new virus remained infectious but could produce less new virus in a limited time. Thiouracil in low concentrations inhibited growth of several plant root systems (24). Reversal was accomplished by uracil but not by thymine, auxins, nucleic acids, thyroxine, or iodide.

Van Asperen (217) found rapid metabolism of administered methylthiouracil in cockerels, very little remaining in the body by 24 hr. Excretion accounted for about 50 per cent. Tissue levels were highest during the first 6 hr., and there did not appear to be any specific localization in the thyroid, although occasionally values there were higher than in any other tissue.

Testing a series of thyroxine analogues for depression of thyroid I^{131} uptake in rats, Lawson & Searle (134) found that most of them could be explained by liberation of iodide. A clear exception was Maclagan & Wilkinson's *n*-butyl-3,5-diiodo-4-hydroxybenzoate (BDHB), which besides showed no protective action against thiouracil effects. Brayne & Maclagan (36) also came to the conclusion that BDHB-inhibition of iodine I^{131} uptake was by some mechanism other than liberation of its own iodide. The amount of thyroxine required to produce an equivalent effect was over ten times as great and, as in the experiments of Halmi and of Vanderlaan, the authors were unable to decide between an effect of thyroxine itself or iodide liberated in low percentage. Deltour & Velez (56) showed thyroxine to be about 10^4 times as active as diiodotyrosine, BDHB, and similar compounds at overcoming the goitrogenic effect of PTU. Considering the doses required, except for thyroxine, it is rather strange that the conclusion was reached again that the antigoitrogenic effects were not caused by iodide liberation.

Extrathyroidal synthesis.—Van Dyke (220) observed the presence of typical thyroid cells, even including development of follicles, in thymus glands of thiourea-treated rats. Foster, Van Dyke & Wase (73) have found a 250 per cent increase in thymus uptake of I^{131} in rats following thyroidectomy. Such a development of thyroid "rests" should be further investigated in relation to the general problem of extrathyroid synthesis of thyroxine, although the demonstration by Hum, Goldberg & Chaikoff (117) of thyroid hormone production even after I^{131} destruction of all detectable iodide-concentrating tissue would be expected to eliminate such cells in the thymus.

Tumorigenesis in pituitary and thyroid.—A great deal of interest and attention has been aroused among cancer workers by the I^{131} induction of pituitary tumors in mice. Gorbman (90) has extended his early work by showing that mice on a low-iodine diet could be as completely thyroidectomized with 30 μc. of I^{131} as with 200, but without any pituitary tumors being produced. Thyroxine injection or thyroid implantation prevented induction of the tumor. Furth, Gadsden & Burnett (76, 78) transplanting portions of mouse

I^{131}-induced tumors, have noted that only one strain of tumor could be successfully transplanted into normal mice, the others requiring hypothyroid animals. Prior propylthiouracil treatment of the host did not permit tumor take, in contrast to the use of I^{131}. Surgically thyroidectomized animals should obviously be tried. These tumors were noted to secrete excess TSH, some gonadotrophin, but no ACTH. Production of pituitary chromophobic adenomata has been reported to take place in mice and rats maintained for 18 and 15 months, respectively, on PTU-containing diets (154, 189). In the case of the rats, the most marked alterations in both thyroid and pituitary glands were obtained with a diet containing both desiccated thyroid and PTU, a circumstance not easily explained.

Thyroid tumors have been produced by Morris & Green (155) by transplanting hyperplastic thyroid tissue from thiouracil-treated mice into thiouracil-treated hosts. After many "generations" of such transplants, several have been developed capable of rapid growth and metastasis formation in normal animals. Clausen (47) and Van Dyke (221) have noted changes of early tumor formation after prolonged propylthiouracil administration or treatment with goitrogens plus carcinogens, and Doniach (61) has shown thyroid adenoma and carcinoma after combining I^{131} and methylthiouracil. The possibility that the widespread clinical use of goitrogens as thyroid-inhibiting agents may lead to thyroid cancers is raised by Boulet, Mirouze & Barjon (34). It should be mentioned that cytological alterations indicative of vast turmoil within the cell have often been seen after I^{131} (59), and it sometimes seems purely a matter of personal choice whether such changes are considered precancerous.

Specific effects of I^{131}.—Therapy of the hyperthyroidism in thyrotoxicosis is undertaken with I^{131} because of the nearly specific concentration and retention of iodide in this gland, and radiation damage resulting is largely restricted to the thyroid. Depression of the overactive gland has usually been considered as being attributable to the physical disruption of the irradiated cells; that this can occur is suggested by the finding of a thyroglobulin type of protein present in some plasmas after therapeutic doses of I^{131} (174, 213). However, several groups have recently reported functional and histological changes in I^{131}-treated thyroids indicative of a far more specific attack. Kurland, Freedberg and associates (75, 131) obtained depressed iodide uptakes and increased iodide turnover as early as one week after therapeutic I^{131}, although no structural changes were observed in representative glands this early. These authors and Dobyns, Chapman, Maloof and co-workers (44, 146), studying both rats and human patients, have found functional and morphological changes progressing in the thyroid for many months after all detectable radioactivity had disappeared. Some of this effect may result from a continuing decrease in blood supply resulting from fibrotic reactions in and around blood vessels.

Kirkland (127) reported flattening of a tracer dose of I^{131} followed by nearly complete KSCN discharge of activity by eight weeks after therapy. Kurland, Freedberg & Fishman (131) found that the therapeutically de-

pressed thyroid could be aroused by TSH injections as long as eight weeks later. Werner, Hamilton & Nemeth (231) observed that several doses of "tracer" quantities of I^{131} would produce temporary remissions in thyrotoxicosis. Although none of these reports is definitive, they all point to the possibility of a specific point of attack of radioiodine.

Actions of the Thyroid Hormone

General, stress.—With the plethora of material discussing the innumerable physiological changes which are related in one way or another to the thyroid, selection has been made not only on the highly arbitrary basis of personal interest (as the editors suggested), but also in an attempt as much as possible to select topics which seemed to have the closest bearing on explaining the action of the thyroid hormone.

Eartly & Leblond (62), studying the effects of administration of physiological doses of thyroxine to male rats of various ages after thyroidectomy or hypophysectomy, have evolved three categories of thyroxine effects. First were those occurring in the absence of the pituitary: increased O_2 consumption, acceleration of heart, thinning of epidermis; second, those not occurring without pituitary: body growth, sexual development, adrenal growth, believed to be attributable to thyroxine influence on secretion of growth, gonadotrophic and adrenocorticotrophic hormones; third were those partially dependent upon the hypophysis, as splanchnomegaly. These actions are undoubtedly more interrelated and less distinct than the report would imply.

Goldstein (89) found that sodium azide ($2\times10^{-3}M$) would return to the control level of metabolism tissues stimulated by various *in vitro* means as well as tissues from hyperthyroid animals. Since formation of organic phosphate was also brought back to resting levels, the author concluded that the thyroid hormone primarily controlled high energy phosphorylations. For some time, this has been Lardy's thesis, although primarily formulated from *in vitro* enzyme reactions.

Wertheimer & Bentor (232) found thyroxine secretion to be an important component of the effect of cold exposure of rats on augmenting glycogen synthesis by diaphragm and concluded that thyroxine had a rapid effect (1 to 4 hr.) on carbohydrate metabolism in addition to a slower influence on the BMR. Although Weiss (226) did not directly correlate the changes with thyroid activity, all of the tissues of six-week-old rats exposed to 5°C. which showed increased Q_{O_2}'s (liver, heart, diaphragm, and kidney) also responded to thyroxine, in contrast to brain which was influenced by neither cold nor thyroxine. This relationship cannot explain why the Q_{O_2} of tissues, except for liver, from six-month-old rats was not increased by cold, since older animals survive cold also. Clark *et al.* (46) also found that 10-weeks' exposure of adult rats to cold increased liver metabolism.

Two reports concerning survival of whole-body irradiation and thyroid status indicate that either hypo- or hyperthyroidism decreased the animals' resistance, the former by prolonging the irradiation leukopenia and anemia,

whereas accelerated metabolism seemed to increase sensitivity to x-ray (126, 129). Administration of desiccated thyroid to rats exposed to 94 per cent O_2 shortens the onset of symptoms of pulmonary damage and increases the severity of pulmonary damage (23). Protection afforded by hypophysectomy was counteracted by desiccated thyroid.

Cook, Jensen & South (50) produced acute shock in rats from burning, freezing, and ischemia. From a comparison of metabolism of liver slices in Ringer's in normal serum, and in serum from shocked animals, the authors concluded that some material accumulated in liver and in plasma which accelerated metabolism. The problem of metabolism-stimulating substances in serum recurs and is difficult to separate from substrate effects, but intrinsic changes in the liver were also indicated.

Effects on embryonic development.—Beyer (27) found 0.025 μg. thyroxine produced consistently greater wet and dry weights of chick embryos from the fourth day on, and total incubation time was diminished by 1 to 1.5 days. Oxygen consumption per gm. wet or dry weight was the same as controls at the same stage of incubation. Vidal (225) injected 5 μg. of thyroxine (which Beyer found highly toxic) into the seven-day chick embryo and noted weight decrease and high mortality. The most marked effects on development seen during the last week of incubation were accelerated changes in the vitellin membrane, increased consumption of yolk material, and hatching time decreased to 20 days.

Roth (183) reported that PTU at a concentration in the aquarium water of 1:2000 was fatal to *Rana temporaria* larvae, but accelerated metamorphosis at 1:10,000. It had no effect on *Alytes obstetricans* between 1:5 and 1:10,000. Propylthiouracil was not able to block thyroxine-accelerated metamorphosis of these forms but caused some modifications. Sluczewski & Roth (194) showed that the thyroxine effects on axolotl could be blocked by estrogen injected prior to the thyroxine. When Jones, Gibson & Nickolls (124) placed zebra fish embryos in low concentrations of thyroxine, pigment formation and general morphogenesis were retarded, while metabolism was accelerated. The opposite effects were obtained with thiouracil. Kaltenbach (125) has studied extensively local metamorphic stimulation by thyroxine pellets implanted in tadpoles.

Humphreys (118) found that hypothyrodism induced in young guinea pigs by methylthiouracil starting in utero had no effect on growth curves or skeletal development. Only slight depression of growth of guinea pigs, and no effect on the weights of many vital organs, was seen by Brown & Young (39) with PTU administration. Whether this indicates resistance on the part of guinea pigs to thiouracils or inadequate dosage is not clear.

Triiodothyronine.—The most dramatic occurrence in the thyroid field since the discovery of thyroid-inhibiting compounds was the demonstration by Gross & Pitt-Rivers (99) that a previously unidentified spot on radiochromatograms of various tissues was 3′,3,5-triiodothyronine (TRIT). Isolation of this compound, simultaneously announced by Roche *et al.* (176), plus

TABLE I

RELATIVE ACTIVITIES OF TRIIODOTHYRONINE AND THROXINE

Evaluation	Ratio: L-triiodothyronine / L-thyroxine
GOITER-PREVENTION IN RATS	
Gross & Pitt-Rivers (99)	3.5–5
Tomich & Woollett (212)	7.4
Colville & Bonnycastle (49)	6.2
Heming & Holtkamp (112)	3.5
O_2 CONSUMPTION, NORMAL RATS	
Gemmill (83)	1
Gross, Pitt-Rivers & Thibault (single dose) (102)	2
Colville & Bonnycastle (49)	2.8
Tomich & Wollett (212)	5.1
Heming & Holtkamp (112)	1 –3.5
Maclagan, Sprott & Wilkinson (mice) (143)	1 –2
ANOXIA, MOUSE	
Tomich & Woollett (212)	4.5
Gemmill (83)	1
Anderson (10)	3 –5
O_2 CONSUMPTION, THYROIDECTOMIZED RATS	
Gross, Pitt-Rivers & Thibault (repeated) (102)	5
Colville & Bonnycastle (49)	2.8
Heming & Holtkamp (112)	>3.5–3.5
Deltour & Karamourtzounis (55)	1 –3.5
TISSUE METABOLISM, THYROIDECTOMIZED RATS	
Wiswell *et al.* (diaphragm, liver) (238)	1.5
BMR, MYXEDEMA PATIENTS	
Asper, Selenkow & Plamondon (12)	5 –10
Rawson *et al.* (170)	1
Blackburn *et al.* (28)	1
Lerman (138)	4 –5
Gross, Pitt-Rivers & Trotter (103)	4 –5
ACCELERATION OF TADPOLE METAMORPHOSIS	
Roth (184)	5
Shellabarger & Godwin (191)	3.8
GALACTOPOIESIS IN COW	
Bartlett *et al.* (22)	>1
INHIBITION OF RELEASE OF THYROIDAL I^{131}	
Anderson (10)	3 –5
MAINTENANCE OF GROWTH, THYROIDECTOMIZED RAT	
Gross & Pitt-Rivers (100)	5
PREVENTION OF PITUITARY CHANGES FROM THIOURACIL	
Gross & Pitt-Rivers (100)	>1.5

proof of its biological activity, has set off a flurry of reports. For convenience, comparative studies of thyroxine and triiodothyronine are summarized in Table 1. There is no doubt that the new compound is as active as thyroxine, but there is considerable discusssion as to whether it is more active. The earlier reports that triiodothyronine was active without any latent period appear inaccurate.

The principal question now seems to be whether thyroxine is deiodinated to TRIT before exerting its metabolic effects[3]. Although Hogness, Van Arsdel & Williams (115) were unable to detect triiodothyronine-I^{131} in rat liver, kidney or muscle from ½ to 24 hr. after injection of thyroxine-I^{131}, Flock & Bollman (71) found TRIT in plasma and tissues of hepatectomized rats after thyroxine injection. Albright, Larson & Tust (9) were able to show formation of TRIT by incubating kidney slices in Ringer-phosphate-glucose solution containing thyroxine. Since the incubation was continued for 9 hr. after TRIT was first demonstrated without any increase in oxygen consumption of the tissue, this experiment also shows that the establishment of an *in vitro* response to thyroxine has not been resolved by TRIT.

Lerman, Harington & Means (139), summarizing much work on thyroxine-like analogues, pointed out that, except for TRIT, modification of thyroxine structure decreased metabolic activity in human myxedema. Kroc *et al.* (130) found that soluble thyroglobulin was equally effective on metabolism of rats whether administered intravenously, subcutaneously or intraperitoneally, whereas the oral route was always less effective. In terms of its thyroxine content, thyroglobulin was over three times as active as L-thyroxine administered by the same route. It seems doubtful if this can be explained on the basis of TRIT, considering the small quantities present in the thyroid.

Barker *et al.* (18), and Wilkinson, Sheahan & Maclagan (236) have compared the thyroxine-inhibiting capacities of many analogues of the hormone. Spurred by the concept that thyroxine activity was mediated by TRIT, Wilkinson & Maclagan (234, 235) have linked the thyroxine-inhibiting properties of BDHB[3] to interference with deiodination: thyroxine activity should be diminished if it were not transformed into TRIT, and TRIT should be enchanced since its deiodination product, diiodothyronine, has no activity. A direct contradiction was presented by Roche, Deltour & Michel (175), who reported that BDHB accelerated, instead of diminishing, urinary I^{131} from labeled thyroxine in thyroidectomized rats. The compound studied the most, BDHB, was tested in thyrotoxic patients for 14 to 75 days, but had no more activity than the corresponding amount of iodine and did not exert a measurable antithyroxine effect when 1 gm. per day was administered to a myxedematous patient maintained on 1 mg. thyroxine per day (74).

Tissue metabolism.—It is now well established that many tissues, particularly of mammalia, exhibit changes in their metabolic rates paralleling the level of thyroid secretion of the whole animal. Since these forms are dependent upon oxygen, energy turnover can be equated to oxygen consumption. The suprising point is that there are many tissues, as reported by Barker &

Klitgaard (19), and Barker & Schwartz (20), which do not appear to be under thyroid control. Included in this category are brain, testis, seminal vesicle, prostate, ovaries, uterus, lymph nodes, thymus, and spleen. No common denominator has yet been found to account for this difference, particularly in the case of the brain, which so clearly is hypofunctional *in vivo* in hypothyroidism. Hoexter (114) has confirmed the lack of change in rat brain Q_{O_2} during six weeks post-thyroidectomy, during which time liver metabolism dropped 20 per cent. *In vivo* studies of myxedematous, and hyperthyroid patients using cerebral blood flow and arterio-venous oxygen differences corroborated the absence of thyroid control over cerebral oxidative metabolism (144, 198). Woodbury *et al.* (242) have found that thyroxine in rats decreased the threshold for electrical and chemical seizures, and diminished the duration and hastened recovery from maximal electrical seizures. Thyroidectomy or PTU treatment produced the opposite. Some indications of similar effects of thyroidectomy and thyroxine-injection were obtained by Domino & Minz (60). It is logical enough to suppose some sort of thyroid control of central nervous system action, but it is certainly not gained through metabolic changes.

Ullrick & Whitehorn (216), rendering rats hyperthyroid by the *ad lib.* feeding of a diet containing desiccated thyroid, reported no effect on the Q_{O_2} of skeletal or intestinal smooth muscle, previously established as sensitive to thyroidectomy and thyroxine injection. They did find an increase with diaphragm but a much greater response from the ventricles of the heart than from the auricles. Thyroglobulin injected into five-day chicks increased the Q_{O_2} of skin over 50 per cent in 24 hr. (104). Sternal bone narrow metabolism was depressed 21 per cent in myxedema (30).

Thyroidectomy was shown by Grad (95) to have a more pronounced effect on depressing oxygen consumption and heart rate in young rats than in old. It is thus understandable that the usual decline in these activities during aging was eliminated by thyroidectomy. Balogh and co-workers (15) studied thyroidectomized rat BMR's for 2 to 3 hr. before and 4 to 5 hr. after injection of thyroxine. In the dose range of 1 to 10 μg., metabolism increased 25 per cent in the first hour and was back to normal after three hours, while 200 to 300 μg. produced no effect in this length of time, having a much longer latent period. While discussions may rage as to desirable experimental doses in relation to physiological secretion level, most workers have been quite unable to find clear-cut oxygen consumption changes without any latent period and from a single small dose of the order of 1 to 10 μg.

Although antimony had little effect in the form of trioxide on rats or rabbits, Westrick (233) found it to enhance the metabolic effect of thyroxine in both animals. Antimony in the thyroid reached concentrations 1.5 to 8 times as high as in any other tissue.

Goldberg & Mayer (87), reviewing the metabolic background of their hereditary obese mice, point out a normal thyroid histology, despite lower oxygen consumption (not surprising in view of over 100 per cent increase in weight, 90 per cent fat), high sensitivity to exogenous thyroxine, and high serum cholesterol. Thiouracil administration to nonobese siblings did not re-

sult in obesity and thyroid I^{131} uptakes of obese and nonobese siblings were the same.

Enzyme action.—Studies on the enzyme systems affected in the animal by thyroid hormone revealed increased carbonic anhydrase of blood of thyrotoxic patients (80) and decreased coenzyme A of thyroidectomized rat liver, heart, and intestine, increasing with subsequent thyroxine injections (205). There was no effect of thyroidectomy on the already low brain coenzyme A, but thyroxine increased it. No *in vitro* effect of thyroxine was obtained. Mathies, Goodman & Palm (149) encountered no effect of thyroxine on spleeen acid or alkaline phosphatase or hepatic alkaline phosphatase, but a reduced renal and increased tibial alkaline phosphatase when thyroxine was injected into hypophysectomized rats. Gaebler & Mathies (79) noted no alteration in liver L-glutamic dehydrogenase when normal or hypophysectomized rats were injected with thyroxine.

Lipner & Barker (141) and Aebi & Abelin (2) found the major part of the hepatic succinoxidase in the mitochondria whether the animals were eu-hypo-, or hyperthyroid. When thyroxine was injected as a single dose into thyroidectomized rats, the liver succinoxidase was elevated at 12 hr. and continued to rise. Smith & Williams-Ashman (197) reported increased liver succinoxidase and adenosinetriphosphatase, and muscle hexokinase, but no change in brain hexokinase or liver choline oxidase in rats made hyperthyroid by thyroxine injection. Although a wide variety of trials was made, thyroxine, thyroglobulin, or iodocasein added *in vitro* had no influence on muscle or brain hexokinase, liver succinoxidase, choline oxidase or adenosinetriphosphatase, or heart succinoxidase.

Continuing work on thyroxine as a member of oxidation-reduction systems, Gemmill (81) has shown that the hormone accelerated the ascorbic acid-ascorbic oxidase system, although interfering with copper oxidation of ascorbic acid, probably through chelate formation. Gemmill set up conditions different from those usually used for succinate oxidation by rat heart homogenate, and found a marked effect of adding thyroxine or thyroglobulin (82, 84). Wiswell *et al.* (238) have confirmed this finding for triiodthyronine as well as for thyroxine. Estabrook and co-workers (64) reported similar results, but were able to duplicate them by addition of calcium. Since calcium appears to activate succinoxidase, thyroxine may be able to bind some Ca in the presence of the greatly elevated phosphate concentration. Further studies on liver homogenate systems by Radsma, Golterman & Birkenhäger (168) have shown thyroxine inhibition of oxygen consumption with lactate and ascorbate, and stimulation with succinate plus cytochrome C.

Evidence continues to be accumulated concerning phosphorylation reactions. Maley & Lardy (145) extended their previous observations on thyroxine "uncoupling" of oxidation and phosphorylation to TRIT. Martius & Hess (147) obtained much lower esterification of phosphorus by mitochondria of hyperthyroid animals, but were unable to show any effect of thyroxine added *in vitro* until after an hour's incubation. Bain (14) has also

confirmed the uncoupling effect of thyroxine; he considered magnesium involved, possibly as an agent reversing the thyroxine effect. The uncoupling concept is difficult to accept as the explanation for thyroxine action on energy metabolism for many reasons, primarily that the experimenters interested in phosphorylation rarely can demonstrate any rise in oxidations associated with the blocking of phosphorylation. In fact, it is seldom possible even to study the two simultaneously. Furthermore, it has never been made clear from an energetics standpoint why such an uncoupling theoretically should increase rather than decrease metabolic rates. Other discrepancies are that thyroglobulin, D-thyroxine, and DL-thyroxine are as active as L-thyroxine.

Using an elegant plethysmographic method of following constriction of swine carotid arteries, Smith (196) has shown a diminished response to epinephrine and acetylcholine in thyroidectomized animals and a return to normal upon addition of thyroxine to the perfusate; the histamine responses were reversed from the above. The addition of the specific enzyme inhibitors ephedrine, physostigmine, and stilbamidine led to increased vasoconstriction and prolonged reaction time to epinephrine, acetylcholine, and histamine, respectively. In very young swine and in animals killed in the winter (195), responses similar to thyroidectomy were obtained; as far as the seasonal change, this is the opposite of the usual reaction to cold exposure.

Spinks (200) linked the greater *in vivo* effectiveness of epinephrine on blood pressure of hyperthyroid rabbits to a lower blood vessel amine oxidase, actually demonstrated only for aorta. Spinks & Burn (201) also showed increased oxidase activity present in liver of thyroidectomized animals and its reversal by desiccated thyroid administration. Thibault and co-workers (cf. 209) have published extensively on production by isolated intestine of a substance from thyroxine, identified in the course of six-years' work as thyroxamine. This material, in concentrations even below the physiological levels of thyroxine, enhanced the epinephrine inhibition of spontaneous intestinal activity. The possibility that thyroxamine is also an inhibitor of amine oxidase should be investigated.

Schneckloth, Kurland & Freedberg (186) have carefully quantitated the increased pressor response to norepinephrine exhibited by thyrotoxic patients or by euthyroid and hypothyroid persons following desiccated thyroid or thyroxine administration. Peltola (159) showed that hyperthyrodism produced in mice lowered the lethal dose of epinephrine by a factor of seven. Addition of desiccated thyroid or iodocasein to the diet of weanling rats halved the epinephrine content of the adrenals and B_{12} partially returned this to normal (57). Holtkamp & Heming (116) interfered with the thyroxine elevation of metabolic rate in rats by administration of the adrenergic blocking agent Dibenzyline (N-phenoxyisopropyl-N-benzyl-β-chloroethylamine HCl). Brewster, Isaacs & Osgood (37) found that total sympathetic blockade decreased the elevated oxygen consumption, heart rate, and cardiac index in experimentally hyperthyroid dogs to the levels encountered in blocked euthyroid dogs. When epinephrine or norepinephrine was infused at specified

rates in blocked hyperthyroid animals, greater increases in the items mentioned were seen than from the same doses in blocked euthyroid. The authors concluded that the principal effect of thyroxine was to augment the responses to epinephrine and norepinephrine.

Lipner *et al.* (142) found consistent intracellular distribution in liver of metabolism-stimulating doses of labeled thyroxine paralleling the protein content of the particles. Since mitochondria carrying (or containing) tagged hormone lost activity readily upon equilibration with nontagged liver homogenates, no specific linking of thyroxine to mitochondria could be demonstrated, perhaps because of the large quantity of thyroxine employed. Lee & Williams (137) injected truly physiological amounts of labeled thyroxine and I^{131}-labeled insulin, but did not consistently submit the liver to cold Ringer's perfusion, a step necessary to eliminate contamination with blood. Binding of the insulin seemed more consistent than of thyroxine.

In order to provide a few references to some important thyroid topics omitted from the review because of lack of space, these are: cholesterol metabolism (148, 182, 210), lipoproteins (140, 204), reproduction in the female (163, 199), reproduction in the male (111, 245), digestion and absorption (67, 185, 187), TSH determinations (52, 158, 206), entero-hepatic movements of thyroxine (5, 38), conjugation and biliary excretion of thyroxine and triiodothyroxine (128, 179, 207), and erythropoeisis (51).

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REPRODUCTION[1,2]

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A number of volumes pertaining to the subject have appeared during the year. These include Bishop's *Recent Advances in Endocrinology*, seventh edition (1); *Glandular Physiology and Therapy*, fifth edition (2); the volume *Hormones in Heath and Disease* (3) containing papers presented at the Anual Graduate Fortnight of the New York Academy of Medicine; the *Year Book of Endocrinology* edited by Gordan (4); *Clinical Endocrinology* by Pashkis, Rakoff & Cantarow (5); *Metabolism of Steroid Hormones* by Dorfman & Ungar (6); *Mammalian Germ Cells*, edited by Wolstenholme (7); and volumes 9 and 10 of *Recent Progress in Hormone Research*. Volume 9 (8) represents papers presented at a conference on steroid determinations while volume 10 (9) contains the proceedings of 1953 Laurentian Hormone Conference.

Hypophysis and Gonadotrophins

Studies designed to determine the nature and content of gonadotrophins in the hypophysis, blood, and urine indicate the continued uncertainty regarding the identity of separate hormonal factors. Thus, experiments with pituitary extracts and transplants in guinea pigs could be interpreted on the basis of effects induced by FSH[2] and LH[2] or through quantitative differences in the effect of a single hormone (10, 11). Studies of the gonadotrophin content of human pituitary tissue indicate absence in infants, small amounts in children (approximately one-tenth the adult levels), with increasing amounts as puberty occurs (12). In adult men FSH and LH were present in equal amounts in hypophysial tissue, but in urine relatively minute amounts of LH compared to FSH were detected (13). Gonadotrophin assays in various pathologic states related to pregnancy have varied usefulness and generally should be done with serum rather than urine (14). The value of the earthworm in pregnancy tests has been discounted (15), but it is claimed that the earthworm is more sensitive than frogs or toads to pituitary gonadotrophin (16).

Confirmation has been given by Palla (17) for the usefulness of the periodic acid-Schiff procedure in studies relating to pituitary histophysiology and localization of hormone production, while Aron *et al.* found that implants of pituitary tissue containing predominantly basophilic or acidophilic cellular populations failed to reveal significant differences in hormonal contents (18). Siebert & Stark (19) studied cell fractions of human placentae and reported that the nuclear fractions contained most of the gonadotrophin. Hypophy-

[1] The survey of the literature pertaining to this review was concluded in early August, 1954.

[2] The following abbreviations have been used in this chapter: FSH (follicle stimulating hormone); LH (luteinizing hormone).

sectomy on the twelfth day in pregnant rats caused a distinct decrease in fetal weights and a lesser effect on placental weights (20).

The inhibitive and stimulatory effects of various procedures on pituitary activity has been the subject of numerous papers. Alloiteau & Courvoisier (21) found that certain hypothalamic lesions caused permanent oestrus in rats and attributed the effect to lack of prolactin. Merklin (22) observed that female mice injected on the tenth day of life with 1 mg. estradiol diproprionate showed no impairment of fertility when tested at the age of 18 to 25 weeks, but that those injected with 10 mg. usually were infertile. A less permanent effect of estrin injections was noted by Emmens (23) in young adult mice. Paesi (24) found that variation of the dose of estradiol benzoate in young rats produced different effects. He considered the possibility that estrin has two or three different actions on the hypophysis, each action having a certain minimal effective dosage level. Zahler (25) studied a series of steroids for their androkinetic, spermatogenic, and pituitary-depressant effects and found no general agreement between the activities of the various compounds. According to Bedoza & Jimenez (26) the administration of estrogen to pregnant women elevated the level of blood gonadotrophin while progesterone diminished it. In this instance, presumably, placental gonadotrophin is primarily involved. On the other hand, Ladman & Runner (27) in a study of the gonadotrophin content of mouse pituitaries during pregnancy found that fluctuations occurred with maxima at 12.5 and 15.5 days of pregnancy. On the basis of statistical analysis, they state that a 10 per cent variation in gonadotrophin content can effect a variation of 82 per cent in responsiveness of the assay animals. No significant differences in pituitary cytology as demonstrated by trichrome staining could be detected. In cases of pregnancy toxemia, an increase in gonadotrophins during the later stages is considered to be of hypophysial rather than of placental origin, while a low gonadotrophin titer in eclampsia is regarded as resulting from a hypophysial circulatory disturbance (28, 29). Matteini & Guisti (30) suggest that the administration of vitamin A has a stimulating effect upon gonadotrophin activity in cases of hypogenitalism.

Modification of pituitary activity through presumed neurogenic pathways have been reported by Moore & Nalbandov (31) for the sheep and Barnes (32) for woman. DeGennes *et al.* (33) suggest that gynecomastia is a result of disturbances of hypophysial function sometimes operating through the diencephalon. Thomson (34) reported convincing evidence that, contrary to earlier reports, onset of estrus in the ferret does not depend upon intact optic pathways. Zuckerman (35) has provided a comprehensive review of relationships between the hypothalamus and the hypophysis.

Schiller *et al.* (36) and Leroy (37) report findings in rats and fowl that can be interpreted as indicating a depressing effect of cortisone on gonadotrophin secretion. On the other hand, the observations of Maddock *et al.* (38) on men injected with cortisone provide evidence that the output of FSH may be increased.

In women who had been hysterectomized, the administration of various gonadotrophins was reported as showing that hypophysial FSH caused no increase in urinary levels of estrogens and 17-ketosteroids, while chorionic gonadotrophin did invoke increases in the levels of each of these (39). Similar increases after chorionic gonadotrophin in menopausal women was reported by Moracci (40). The latter observer found that estrogens reached a peak after 24 hr., while the peak for 17-ketosteroids occurred after 72 hr., a finding that recalls earlier observations on men (41, 42).

Much remains to be done to demonstrate the manner of action of lithospermum extracts in interfering with the effects of gonadotrophins. Reports by English & Noble (43) and Graham & Noble (44) indicate that the inactivation of gonadotrophin by lithospermum is not the same as by periodic acid and that extracts of lithospermum contain a substance, removable by dialysis, which interferes with the inactivating principle.

Reproduction in the Female

Ovary.—The chemical composition of human ova during maturation and atresia was studied by Hedberg (45) primarily with x-ray radio-micrographic methods. Using various histologic and histochemical procedures Nishizuka (46) studied ovaries from numerous species and concluded that in all the theca interna cells are the source of estrogen. After corpus luteum formation, the theca lutein cells continue to produce estrogen while the granulosa lutein cells are responsible for secretion of progesterone. Interstitial gland cells are said to be similar in structure and function to theca interna cells. Studies on phosphatase in the ovary and genital tract have been reported by Moschino & Parisotto (47) and Goldberg & Jones (48).

The ovaries of virgin mice from eight inbred strains showed distinct quantitative differences (49). Thus C57L mice ovaries show a congenital cystic condition, polyovular follicles are common in C58 females, and C3H, Balb/c, and MA/My mice have the largest numbers of follicles and corpora lutea. Continuous estrus was noted (50) in rats with ovaries transplanted to the tail and was accompanied by increased numbers of basophils and gonadotrophin levels in the hypophyses. In rats thiourea-induced ovarian cysts were prevented by testosterone propionate (51). Ovaries of rabbits and mice were irradiated. In the majority of instances the dosages used (800 to 2000 r for rabbits and 300 to 1500 r for mice) completely destroyed the germ cells (52). In the guinea pig (53) thyroidectomy reduced reproductive capacities, but propyl thiouracil did not, and hyperthyroidism to the point of tolerance appeared to improve reproduction slightly.

Mayer (54) has provided a good review of the histophysiology of the corpus luteum and Green & Zuckerman (55) have shown that in rhesus monkeys the two ovaries contain about the same number of oocytes, the number varying inversely with the body weight and not being significantly different in various stages of the cycle. In cows (56) repeated courses of superovulation with gonadotrophins led to a decline, in successive courses, in the number of

corpora lutea. This could not be related to titers of antigonadotrophins in the sera. Doyle (57) has described and pictured ovulation in women as seen through the culdoscope and reports that denervation of the tubes and uterus in 17 infertile women considered to have tubospasm resulted in 14 conceptions. Although ovarian weights were not changed significantly in rats fed a fat-free diet, evidence of reduced estrogen secretion, accompanied by increased numbers of pituitary basophils, was noted (58). The importance of nutrition in ovarian development in the rabbit was noted by Adams (59) in a study concerned also with recovery and transplantation of ova.

Mechanisms involved in the formation of the first and second polar bodies in the rabbit have been discussed by Moricard & Gothie (60, 61).

Ovarian hormones and accessory organs.—The effects of injected progesterone on ovarian function have not been consistent in different studies. Thus Schlecta *et al.* (62) observed that progesterone had an inhibiting effect on estrus and mating in the rat while studies in the ewe (63, 64) and heifer (65, 66) were interpreted as indicating that progesterone improved fertility by encouraging gonadotrophin secretion. On the other hand, Dauzier *et al.* (67) believe their studies indicate that low doses of progesterone stimulate secretion of gonadotrophins while high doses inhibit the hypothalamic-hypophysial system. Asdell (68) has reviewed procedures and mechanisms by which ovulation can be controlled.

Arteriographic studies in women indicated that estrogen, but not progesterone, increased the size of uterine blood vessels (69). Comparison of the effectiveness of various estrogens in women has been made by Kupperman *et al.* (70) using a numerical conversion factor for the 11 most common menopausal complaints.

Sensitive methods for the assay of progesterone in body fluids and tissues have been described by Edgar (71, 72). It is noteworthy that progesterone could be detected in ovarian blood, but not the peripheral blood of various animals and was found in mature follicles of cows and sows. Edgar suggests that progesterone is active at low serum concentrations and probably is metabolized very rapidly. Steroidal substances in human corpora lutea and placentae have been discussed by Jayle & Crepy (73), lipid changes associated with estrogen production in the rabbit ovary by Claesson *et al.* (74), and lipid changes associated with progesterone secretion in rabbits and women by Andreoli (75).

Biological assays indicate that 19-norprogesterone is from four to eight times more potent than progesterone (76). Effects of estrogen and progesterone on the interstitial tissue of the ovary in hypophysectomized, gonadotrophin-treated, and x-irradiated animals are discussed by Paesi & DeWit (77). Antagonism between the effects of estrogens and androgens can be shown to exist in some, but not all organs (78), and estrogens stimulate mitotic activity in some, but not all epithelia (79, 80).

The use of fluorometric procedures for distinguishing between the various estrogens has been described by Goldzieher (81), the use of deuterium-la-

belled estrone in assessing metabolic conversions by Pearlman *et al.* (82), and a feasible method for the bioassay of estrogens utilizing the chick oviduct by Dorfman & Dorfman (83). The importance of folic acid in the action of estrogens has been further confirmed (84), and Phillips *et al.* (85) relate the effects of folic acid antagonists in inhibiting normal estrogen actions to an interference with the synthesis of nucleic acids.

Hyaluronidase does not affect the spread of intradermally-injected estrone (86). The estronase content of various tissues was determined by Bischoff *et al.* (87) for men, rats, mice, and rabbits. Testicular tissue, particularly in the rabbit, showed very high levels. Progesterone, but not estrone (88) was found to increase the histaminase content of the endometrium in both normal and castrated rabbits. Progesterone also accelerated the rate of phosphate release from homogenized rat liver, the acceleration being proportional to the concentration of progesterone (89).

Estrogenic substances were detected in alfalfa and clover hays in varying amounts (90) and in isoflavone derivatives prepared from soybean oil meal (91). Pigs given dienestrol during the fattening period showed stored estrogenic substances in body fat, but none in muscle (92).

It would appear that response of the symphysis pubis in the guinea pig and mouse depend upon two different relaxin fractions (93). Growth and regression of deciduomata in adrenalectomized rats are comparable to these processes in intact animals (94). In castrated rabbits progesterone alone was not sufficient to permit the deciduomata reaction, but either estrogen or vitamin E provided the necessary supplement (95).

Fertilization.—Emphasis was placed by Chang (96) on the importance for fertilization of physiological integrity of individual spermatozoa rather than on the presence of large numbers in the female tract. He also suggests that the fertilizing capacity of sperm is not fully realized until they have resided in the female tract for several hours. Ova show a sharp drop in capacity for fertilization after four hours postovulation, but do so more slowly when maintained at 0 to 10°C. (97). Smith (98) has discussed the preservation of rabbit eggs at low temperatures, emphasizing the importance of relatively slow freezing. Careful studies by Venge (99) indicate that control of the factors necessary for *in vitro* fertilization of mammalian eggs has not yet been achieved. The factors responsible for early death of ova have been considered by Hartman (100) and Casida (101).

Earlier studies by Barr and his colleagues (102) at the University of Western Ontario on the use of human skin biopsies in distinguishing chromosomal sex have been confirmed (103). Application of the procedure to cases of ovarian agenesis indicate that the majority of such individuals are genetic males (104, 105).

Antifertility agents.—Sanyal (106, 107, 108) has continued his studies on an antifertility factor in *Pisum sativum* and believes it to act as an antiprogesterone and to be related to the hydroquinones. Thiersch (109) has provided further observations on the antifertility effects of folic acid antagonists,

Laszlo & Henshaw (110) have reviewed a large series of plants said to have effects on fertility, and Henshaw (111) has reviewed various means of interfering with reproduction.

Further studies on the effect of nitrofuran compounds in producing spermatocytic arrest in rats (112, 113, 114) have furnished confirmation for earlier observations on the mechanisms through which the compounds act. Hudson & Pino (115, 116) report that enheptin (2-amino-5 nitrothiazole) has adverse effects on fertility in both pullets and cockerels. The possibility that progesterone might be effective under some conditions in the control of fertility was suggested by the studies of Schlecta *et al.* (117). They observed that progesterone in single doses of 5 to 50 mg. inhibited estrus and mating 10 to 19 days while 5 mg. twice weekly provided continuous inhibition. Bollag (118) reported that Myleran (1:4-dimethanesulphonyloxybutane), a compound used in treating myelogenous leucemia, caused destruction of germ cells in male and female rats.

Reproduction in the Male

Testis.—Coste *et al.* (119) have described a progressive decrease in the ascorbic acid content of rat testes from age seven days to adulthood and ascribed it to the effects of gonadotrophin on the testes. Histochemical studies of normal human testes (120) indicated the presence of ascorbic acid, glycogen, and lipid, but not steroids or glycoproteins in the germinal cells. In cases of the Klinefelter syndrome (121) disturbances in the peritubular connective tissues were attributed to defective function of the Leydig cells. The histochemical changes in human testes following treatment with diethylstilbestrol have been described and related to modification of the pituitary gonadotrophins (122).

Albert and his colleagues, in a series of papers devoted to various aspects of human testicular histology and function, have discussed the normal testis (123), the testis in hypogonadism (124), and dwarfism (125) in men with multiple defects of pituitary function (126) and in cases of failure of gonadotrophin secretion during adult life (127). Sohval & Soffer (128) described two brothers whose testicular defects were accompanied by a galaxy of other abnormalities and one case (129) in which they believed Sertoli cell differentiation was imperfect. Other studies on the testis in hypogonadal men include those of Castillo *et al.* (130), Landau (131), and Nelson (132). Weller (133) has confirmed earlier studies on the effectiveness of chorionic gonadotrophin in stimulating the testicular Leydig cells, but not the adrenal cortex.

Bishop (134) has reviewed the endocrine aspects of infertility, and Landau *et al.* (135) believes, on the basis of abnormal eosinophilic responses to epinephrine, that the basis for infertility in some patients resides in disturbed hypothalamic function. Trabucco (136) reported beneficial effects of cortisone on the sperm count of the majority of men treated. The various conditions encountered in testes of infertile men have been described by Nelson (137), and Tourney *et al.* (138) have shown that contrary to earlier reports

specific abnormalities of testicular structure do not occur in schizophrenia. Morris (139) reported on five cases with female habitus in which the gonads were demonstrated to be testes.

The problem of cryptorchidism and its management has been discussed in detail by Bishop (1), Hamm & Harlin (140), Maitland (141), and Grove (142). The importance of early attempts to correct cryptorchidism has been emphasized by the studies of Engle (143), which confirmed the earlier reports of Cooper (144) and Nelson (145) that the germ cell populations of undescended testes tend to decline at an early age.

Studies on the so-called male climacteric (146) have considered the relation between the hormonal levels and the objective and subjective symptoms encountered in association with the syndrome. Emphasis was given to the lack of uniform agreement between gonadotrophin and 17-ketosteroid levels on one hand and the symptomatology of the condition on the other. Thus the only reliable means of distinguishing between the male climacteric and psychogenic impotence was said to be therapeutic trial with androgenic hormone. According to Vinci (147), some cases of psychogenic impotence in young men are associated with diminished levels of 17-ketosteroids.

Several reports have appeared on cases of precocious puberty associated with interstitial cell tumors of the testis (148, 149, 150). As is almost always true in these cases, the tumors were regarded as benign, but in two of the three cases there were suggestions of related adrenal cortical involvement.

Marshall (151) observed remarkable uniformity in the testes of eight species of migratory birds at the time of their arrival in England. Vaugien (152) reported acceleration of spermatogenesis in sparrows exposed to continuous artificial light. In starlings (153) similar stimulation was observed and it was further noted that the presence of female starlings also provided a stimulus for spermatogenesis. On the other hand, the prairie dog testis (154) was not stimulated by exposure of the animal to various periods of light or of controlled temperature.

Spermatozoa and semen.—Factors which influence sperm production have been reviewed by MacLeod (155), and Roosen-Runge and Barlow (156) in a quantitative study of human spermatogenesis concluded that spermatogonia usually undergo seven divisions before differentiation into spermatocytes. Swyer (157) reported improvement of spermatogenesis in men with moderate, but not extreme, oligospermia following subcutaneous implantation of testosterone pellets, and Maqsood (158) considered that his studies showed the importance of thyroxin levels on spermatogenic activity. Seneca & Ides (159) made the surprising observation that oxytetracycline (terramycin) and polymixin were very effective, and penicillin, bacitracin, and carbomycin (Magnamycin) fairly effective in accelerating spermatogenic activity in young adult rats. These studies were based on histologic criteria only and were accompanied by other studies on the effects of various antibiotics on human spermatozoa. Melrose (160) has shown that streptomycin added to bull semen increased the conception rate particularly in bulls of low fertility

performance. Severe damage to the germinal cells of the guinea pig occurred when either autologous or homologous testicular tissue was injected in combination with killed mycobacteria (161).

The well-known effects of elevated temperature on mammalian spermatogenesis have been studied in the bull (162), and a recent report (163) indicates that lowering of testicular temperature to from −6°C. to −8°C. for 1 hr. causes complete and permanent spermatogenic destruction, presumably attributable to vasoconstrictor effects.

Techniques for preservation of sperm at low temperatures have been described for the fowl and bull (164) and man (165). In each instance the importance of adding glycerol to the semen was stressed. In the fowl freezing could be carried out rapidly, but better survival in the case of bovine and human sperm was obtained with slower freezing. The capacity of preserved sperm to fertilize ova has been demonstrated repeatedly for the bull and recently for man (166).

Oettle (167) has provided a comprehensive discussion of changes in human semen after ejaculation. Bunge & Sherman (168) have called attention to the lack of spontaneous semen liquefaction in some men and report that the addition of α-amylase to the semen will provide for rapid liquefaction without damage to the spermatozoa. Further consideration of the problem of semen liquefaction was provided by Lundquist (169).

The importance of a careful analysis of the semen pattern as a guide to diagnosis and therapy has been emphasized by Hellinga (170), and Frank *et al.* (171) have called attention to the frequent occurrence of immature germ cells in the semen of infertile men. Similar emphasis has been given to the importance of careful examination of bull semen (172). In a paper devoted to sperm movements Rothschild (173) called especial attention to the deleterious effects of overdilution upon sperm viability. Similar conclusions were reached by Kok (174).

Lardy (175) and Terner (176) have reviewed the characteristics of metabolism in spermatozoa under various conditions, and the biochemical aspects of seminal fluid have been discussed by Mann (177) and Gassner & Hopwood (178).

Additional information on electron microscopy of human sperm has been reported (179), and the relationship of sterility to abnormal sperm was noted in a strain of house mice (180). Sperm transport to the ovarian area in the cow was reported as taking place in 2 to 4 min. after either mating or artificial insemination (181). The uterine movements involved could be duplicated by the injection of oxytocin.

In a series of papers Austin & Braden have discussed various aspects of spermatozoal behavior and relations in the fertilization process. These include polyspermy (182, 183), relation of sperm and ovum ages to fertilizability (184), polar body formation (185), distribution of nucleic acids after fertilization (186, 187), and a general review of the fertilization process (188).

The testicular content of hyaluronidase in normal, hypophysectomized,

and androgen-treated rats has been studied by Steinberger & Nelson (189). Hypophysectomy radically reduced, and testosterone propionate maintained, the enzyme content; but, contrary to an earlier report, the latter did not elevate it above normal levels. According to Beccari & Zaratini (190), hyaluronidase enhances the effect of serum gonadotrophin in immature female rats.

Androgenic hormone.—Levels of 17-ketosteroids showed increased levels with the onset and progression of puberty (191), paralleling an increase in gonadotrophin titers (192). According to Dobriner *et al.* (193), α-ketosteroid patterns in adult men show levels which indicate that adrenal metabolites vary insignificantly with aging, whereas the level of metabolites derived from testicular precursors diminished in older men. Similar findings were recorded and supported by biological assays for androgenic activity by Hamilton *et al.* (194). Lowered 17-ketosteroid levels were noted in some, but not all, men with disorders of sexual potency (195), the use of a chorionic gonadotrophin test in distinguishing between primary and secondary hypogonadism was recommended (196), and the metabolic effects of androgens and estrogens in cases of primary gonadal insufficiency were discussed (197).

Methods are available for the determination of neutral 17-ketosteroids in plasma (198). The chief constituent was identified as dehydroisoandrosterone with lesser quantities of androsterone and etiocholanolone. In a similar study Gardner (199) found an average of 74 μg. per 100 ml. in adult men and more than 100 μg. in new-born infants with levels diminishing rapidly to zero within a few days. The *in vivo* metabolism of neutral steroid hormone metabolites has been considered in detail (200). The comparative value of various procedures in the hydrolysis of neutral urinary ketosteroid conjugates (201), methods for the colorimetric analysis of urinary 17-ketosteroids (202), and the separation of these by chromatographic procedures (203, to 206) have been described. Procedures involving C^{14}-labelled compounds in the study of steroid hormone metabolism were reported by Heard *et al.* (207) and Gallagher *et al.* (208).

Studies in men with hepatic cirrhosis indicate that the excretion of 17-ketosteroids is reduced (209, 210). Similarly, reduced levels were noted in men with pulmonary tuberculosis (211), and testosterone treatment provided distinct anabolic effects. Less distinct anabolic activity was noted in other conditions following administration of methylandrostenediol (212, 213).

Adverse effects of castration, and improvement following administration of androgen were noted on the respiration of prostatic tissue (214, 215) and on acid phosphatase activity in the seminal vesicle (216). Incubation of red cells with testosterone resulted in formation of 17-keto compounds, but not in the presence of sodium fluoride (217). Addition of either androgens or estrogens to cultures of rabbit fibrocytes inhibited mitotic activity (218).

A relationship between initial comb size and response to androgens in young chicks was noted by Jaap & Robertson (219). Calves treated with testosterone showed a better gain in weight per pound of food and had larger thyroids than their controls (220). Chick mullerian ducts cultured *in vitro*

behave as ducts *in situ* when isolated after sexual differentiation, development continuing in female and regression occuring in male ducts. Addition of androgen to the culture medium caused regression in female ducts (221). The moderate effects of small doses of estradiol benzoate in inducing intersexuality in male chick embryos was reinforced strongly by the addition of testosterone propionate (222). According to Pasqualini (223) prolactin augments testosterone in stimulating the rat seminal vesicle, the prolactin effect being concerned with increased secretory activity.

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COMPARATIVE PHYSIOLOGY (RESPIRATION)[1,2]

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Oxygen Tensions and Repiration

This review covers selected and strictly comparative aspects in the field of respiration. It contains only few references prior to 1950, and it should not be considered complete. Earlier reviews are by Bishop [(1), general], Prosser [(2), respiratory functions of blood pigments], von Bertalanffy [(3), general], Kleiber [(4), body size], Harnisch [(5), aquatic animals], and by Black [(6), fishes]. Temperature and respiration are not considered because reviews, with emphasis on mechanisms of compensation, are forthcoming [Bullock (7), Precht (8)].

In the "independent" type of animals the oxygen consumption occurs at constant rate above a "critical oxygen tension" (t_c). Below t_c oxygen uptake varies with tension. One would think that zero tension would correspond to zero consumption; still there are reports by Harnisch (9, 10, 11) of anaerobic evolution of gas different from carbon dioxide in aquatic insect larvae and by Füsser & Krüger (31) and Koenen (32) of anaerobic gas uptake and evolution. Judgment must be withheld till demonstration is made that these gas exchanges do not represent the errors of the different methods.

Independent respiration[2].—For small planktonic single larvae (0.4 mm.) of the worms *Phyllodoce* and *Pectinaria* and for swimming veliger larva (0.2 mm.) of the clam *Mya arenaria* Zeuthen (12) found t_c 40 to 50 mm. Hg at 16°C. The experiments were on single animals in microrespirometers, and the curves are interpreted to approximate the relation between tissue oxygen tension and tissue oxygen consumption. Below t_c the ciliary activity decreases with oxygen tension and with consumption. In the adult oyster (*Ostrea edulis*) Gaarder & Eliassen (13) found t_c to be 100 mm. Hg at 22°C., in the rheophilic snail *Ancylus fluviatilis* [Berg (14)] t_c was about 80 mm. Hg at 16°C., and in the final instar larva of *Chironomus plumosus*, subspecies *plumosus*, Walshe-Maetz (15) found t_c about 80 mm. Hg at 17°C. The larvae were acclimatized to life in small glass tubes suspended in water of the oxygen tension of the particular experiment simulating conditions in the natural habitat. In two chironomids (*C. longistylis* and *Anatopynia varia*) from a ditch where the oxygen tension in the summer never rose above 92 mm. Hg and where in the night it might drop to a minimum of 3 mm., Walshe (16) found

[1] The survey of literature pertaining to this review was completed in May, 1954.

[2] The following abbreviations have been used in this chapter: t_c (critical oxygen tension); ACTH (adrenocorticotropin); hb (hemoglobin); W (soft body weight); b (exponential relation of O_2 consumption to body weight).

t_c 35 to 65 mm. Hg. at 17°C. The two species were studied outside their tubes in a slowly rotating syringe. Parasitic protozoa and certain small helminths are sometimes independent down to very low oxygen pressures [von Brand (17]: *Trypanosoma cruzi* (t_c 38 mm. Hg), *Plasmodium knowlesi* (t_c <38 mm.), *Temnocephala* spp. (t_c <8 mm.) and *Trichinella spiralis* (t_c <8 mm.). The diapausing silkworm (*Platysamia cecropia*, 25°C.) is independent from 0.05 to 1 atm. oxygen and shows a slight decrease in rate of oxygen consumption at 2.7 atm. [Schneiderman & Williams (18)].

Dependent respiration.—The rate of oxygen uptake varies with oxygen pressure from zero to or above the oxygen pressure of air. The consumption /pressure curve is linear, it may gradually level off at high pressures, or there may be a sharp bend reminiscent of a "critical point." Dependent respiration was observed for a number of helminths (*Fasciola hepatica*, adults; *Diphyllobothrium latum*, plerocercoids, proglottids; *Asccaris lumbricoides*, adults) for tensions from 8 to 760 mm. Hg (17). With the possible exception of Laser's study on Ascaris which shows exceptionally high values at 760 mm., the dependency is steeper below than above 160 mm. Hg, this tension being reminiscent of t_c. According to Bueding (19) the small filarial nematode *Litomosoides carinii* and the parasitic trematode *Schistosoma mansoni* show dependent respiration. *Schistosoma* dry weight is only 0.024 to 0.057 mg. [Bueding (20)], so dependency does not always reflect large body size and diffusion hindrance. Hayes, Wilmot & Livingstone (21), in work with salmon eggs, define the critical tension as the one at which Q_{O_2} is half maximal. With the present definition of t_c their results rather demonstrate dependency in the whole range from saturation with air to zero oxygen tension. Below saturation with air (160 mm. Hg) Walshe (16) found oxygen uptake to vary with tension in two rheophilic chironomids, *Tanytarsus brunnipes* and *Anatopynia nebulosa*. The two species were from the mud in a stream where the oxygen tension never dropped below 125 mm. Hg. All chironomids are tube dwellers [Walshe (22, 23)] which irrigate their tubes intermittently and hence are in a position to control their oxygen supply to some extent independently of the oxygen content of the water in which they live. The present dependency is for animals outside their tubes and cannot, therefore, straight away be accepted as valid for the natural habitat. This becomes very clear from a later contribution by Walshe-Maetz (15). For the fresh water snail *Ancylus fluviatilis*, Berg (14, 24) does not agree with the statement (16) that rheophilic animals generally show dependent and, in air-saturated water, unusually intense respiration. Being within a shell, potentially a very effective diffusion barrier, *Ancylus* is in a more natural habitat than are the chironomids outside their tubes, and the two sets of experiments should not be compared. *Acroloxus lacustris*, a snail from stagnant fresh water where the oxygen tension drops to, and perhaps below, 90 mm. Hg, shows dependent respiration (14). In *C. plumosus plumosus* living in glass tubes there is dependency below air saturation (15). During acclimation (5 hr.) in half-saturated water the rate increases 75 per cent and the dependent curve changes into an

independent one. At the same time the irrigation activity of the animal increases. Also in other aquatic insects the acclimation time has been reported to be a significant factor when decision should be made about dependent versus independent type of respiration [Harnisch (25 to 28)]. This is at least partly attributable to tracheolar regulations. In *Prodiamesa olivacea* the tracheoles show more and thinner ramifications after than before anaerobiosis [Harnisch (27, 29)] with maximum development in cases of maximum respiration, induced by previous anaerobiosis, and resulting in death ["entfesselte Erholungsatmung," Harnisch (30); cf. also reference (73)].

Füsser & Krüger (31) for two pulmonate snails studied in moist air (*Planorbis corneus* and *Limnea stagnalis*) observed linearly dependent respiration between 21 and 5 per cent O_2. Below 5 per cent *Planorbis* becomes independent (thanks to circulating hemoglobin, independency ruined by 5 per cent CO) but in *Limnea* the respiration drops off more steeply. Thus, in both species 5 per cent (31 mm. Hg) is reminiscent of a critical point below which the one regulates more successfully than the other. The submerged *Limnea* comes to the surface for breathing when the oxygen in the lung drops below 6 per cent. It has bearing on the discussion, referred to above between Berg (24) and Walshe (16), that the respiratory rate measured in the submerged snail—with free access to the surface—is only about one-third to one-half of that measured in air, even though the average oxygen tension in the water is not much below air saturation. Low oxygen in the tissues is not a strong stimulus for breathing. The small worms *Tubifex tubifex* and *Limnodrilus claparèdeanus* when outside their tubes creep together in groups, and this results in considerable metabolic depression [Koenen (32)]. It remains uncertain whether the depression should be attributed to lower activity or to active partial quenching of the respiration. The technique is not satisfactorily controlled. Still, the absence of regulation from the side of the animals against insufficient supply of oxygen is remarkable. Seven species of Hawaiian crustaceans weighing from 2.9 to 12.5 gm. were studied by van Weel, Randall & Takata (33) at 26° to 28°C. The respiration chamber was perfused at constant rate with sea water of varying oxygen contents. In four species (*Pseudozius caystrus*, *Metopograpsus messor*, *Calappa hepatica*, and *Pseudosquilla ciliata*) the percentage utilization of oxygen from the perfusate remained unchanged in the interval between 6.2 and 2.6 ml. O_2/l., indicating consumption in proportion to tension. In two species (*Phymodius ungulatus*, *Platypodia granulosa*) the percentage utilization dropped in the same interval, indicating even steeper drop in consumption with tension. In one, *Podophthalmus vigil*, the only mud-dweller studied, the percentage utilization increased from 6 to 13 per cent as the oxygen content of the water decreased from 4.6 to 3 ml. O_2/l. and it remained almost constant as the content dropped further to 2.5 ml O_2/l. Thus, in this species there is independency (regulation) in the first and dependency (absence of regulation) in the second interval. Below 2.5 ml. O_2/l. there is in all seven species a steep increase in the percentage utilization, compensating, or overcompensating, for

the diminished supply of oxygen. Thus, in these crustaceans the respiration passively follows the oxygen pressure in the water to a certain low tension, when regulation sets in and serves to secure a mimimum amount of oxidation. In the passive range the oxygen consumption varies by a factor 2 to 3. In the lobster *Homarus vulgaris* [Thomas (34)], the oxygen uptake varies linearly with oxygen tension over an even wider range and at all temperatures between 6° and 18°C. No regulation in response to very low oxygen tensions (<1 to 2 ml. O_2/l.) was observed to break this expressed dependency. The Hawaiian crustaceans were allowed ½ hr. of acclimation to each new oxygen tension. The lobster in the course of several hours depleted the oxygen available in a closed system. In neither study was ventilation of gills or abdomen observed to vary in a regular manner with the oxygen content of the water, so the regulation in the Hawaiian species is on the tissue level (the authors' suggestion), in the circulatory system, or it reflects characteristics of the blood pigments. The lobster's response to increased temperature demonstrates capacity for increased ventilation. In eight species of amphipods and isopods (14°C.) Walshe-Maetz (35) found absence of capacity for ventilation control in terrestrial species and maximum control of ventilation in aquatic animals. Marine and brackish species were intermediate. The species were adapted to possible variations which they may encounter in nature. Caddis larvae (*Limnophilus flavicornis*) respond to diminution in oxygen by acceleration of the respiratory movements, but increased carbon dioxide is without effect [Fox & Sidney (36)].

Partial and complete anaerobiosis, oxygen debt.—In *Planorbis*, Füser & Krüger (31) report unchanging R.Q.'s (0.53 to 0.65) when the oxygen of the moist atmosphere changes from 21 per cent to 3 per cent. The metabolic rate drops to 44 per cent of the value in air. Similarly, in *Limnea* R.Q. is unchanged from 0.69 to 0.81 and the metabolic rate drops to 57 per cent. The blood of molluscs carries a considerable alkali reserve [Prosser (2)], so, had the animals produced fixed acids to make up for the oxygen consumption missed at the lower tensions, R.Q. should have been influenced. Von Brand, Baernstein & Mehlman (37), and Mehlman & von Brand (38) for a number of snails observed that (at 30°C.) carbohydrates disappear under conditions of total anaerobiosis, in several cases only slightly faster than aerobically. Those species which are less resistant to oxygen lack (*Lymnea*) produced CO_2 faster than those more resistant (*Australorbis* and *Helisoma*). In all cases the CO_2 was primarily of inorganic origin, in the less resistant species released mostly by lactic acid, in the more resistant primarily by propionic and acetic acid. In continued anaerobiosis, lactic acid, where formed, is excreted more efficiently in the resistant than in the less resistant snails. Epps, Weiner & Bueding (39) for bacteria-free *Ascaris* demonstrated propionic and acetic acid. In *Lymnea* the ratio anaerobic/aerobic splitting of carbohydrate is 1.2, in *Melanoides* 1.4, in *Australorbis* 1.5, in *Helisoma* 4.1, and in *Pomatiopsis* it is 4.5. The high values are as high as in most free-living invertebrates, but the lowest are as low as in parasites. Von Brand & Mehlman (40) transferred

snails (*Australorbis glabratus*, *Helisoma duryi*, *Aplexa nitens*, and *Lymnea stagnalis*) from water of variously defined oxygen tensions to anaerobic conditions and back to pre-anaerobic conditions. Pre-anaerobic and post-anaerobic rates were somewhat dependent on oxygen tension and—despite differences in rate—dependent to about the same extent at 30°, 20°, and 10°C. On a percentage basis the post-anaerobic stimulation was about the same at all oxygen tensions studied. Von Brand & Mehlman find it is difficult to explain these observations in terms of diffusion of oxygen as the only limiting factor, and cautiously suggest that "a possiblity exists that a direct influence of the oxygen tension on cellular processes is underestimated." Absolute oxygen debts are given with reservations because it is difficult to decide when payment is complete. In salmon eggs (21) the normal rate was 392 μl. O_2/2 hr. In 2 hr. of low O_2 only 149 μl. were consumed leaving a deficiency of 243 μl. Back in aerated water respiration slowly returned to normal rate and there was no sign of an oxygen debt. Development was unimpaired. In the first ½ to 1 hr. after return to air-saturated water after 10 to 24 hr. in water deficient in oxygen (30 per cent air saturation) *Ancylus fluviatilis* showed no increase in metabolism relative to controls from brook water (14). The excess oxygen taken up by marine larvae (12) which have been exposed to partial or complete anaerobiosis for several hours is very small in comparison with the oxygen deficiency accumulated. *Chironomus plumosus*, after 16 hr. in nitrogen, accumulate an oxygen debt corresponding to only ½ per cent of the deficiency [Walshe (41)]. Harnisch (10) considers that waste products were not formed in significant amounts, and those were excreted. To him oxygen debts in many invertebrates represent repair work on vital systems rather than resynthesis of metabolites accumulated. In species sensitive to oxygen lack (*C. thummi*) the anaerobic damage is considerable and the oxygen debt ("Sekundäre Oxybiose") impressive. In resistant species (represented by *C. tentans*) the oxygen debt is insignificant and the animals resume full activity immediately upon return to air. These views are expounded in a long series of papers [review with references (10)]. Harnisch also considers that chironomids carry stores of oxygen in peroxides (42) for use in anaerobiosis ("Endoxybiose"). The experimental evidence, though sometimes interesting, scarcely permits such far-reaching conclusions. For the fly *Calliphora erythrocephala* Agrell (43) traced the usual U-shaped curve for oxygen consumption during pupal life and found similar curves for a number of dehydrogenases. Fat was the main energy source (95 per cent), but small amounts of carbohydrates were also degraded. Twenty-four hours in nitrogen blocked fat utilization. Carbohydrate metabolism was stimulated some, but the lactic acid formed accounted for less than 1 per cent of the energy liberated in air. Fifty hours in nitrogen results in 65 hr. delay in emergence of the fly from the pupa. The stability of dehydrogenases during anaerobiosis was considerable. Agrell concludes that anaerobiosis represents anabiosis, and he finds arguments for the view that in nitrogen both anabolic and catabolic processes are blocked. In anaerobiosis sea urchin spermatozoa [Tyler & Rothschild (44)] show neither

significant glycolysis, nor carbon dioxide, ammonia, and urea formation. Amino acids and glycolyzable sugar were present.

In heart muscle slices [Fuhrman, Fuhrman & Field (45)] and in some snails, oxygen consumption occurs at a reduced rate after complete or partial anaerobiosis. The respiration of the slices can be stimulated to some degree by the addition of boiled extracts from a heart not previously exposed to oxygen lack [Lemley & Meneely (46)]. Danes (47) for chick heart fibroblasts grown in Cartesian divers measured Q_{O_2} and $Q^{N_2}_{CO_2}$. Anaerobic CO_2 (assumed to represent lactic acid) accounts for only 40 per cent of the energy liberated in air. There is no evidence of an oxygen debt. The bacterium *Asterococcus mycoides* oxidizes glucose at a high rate, but is unable to split it anaerobically [Rodwell & Rodwell (48)]. In the older literature [Wilhelmi (49)] there are reports for *Torula*, for embryonic heart, for pigeon brain, and for fish retina that the ratio anaerobic/aerobic caloric yield is below unity (0.33, 0.48, 0.41, 0.70 in the cases mentioned). Scholander, Irving & Grinnell (50) long ago observed that the heat production of the diving seal, as evaluated from measurements of organ temperatures, drops to 50 per cent during a dive.

Acclimation to low oxygen pressure.—After a number of exposures of insects to explosive decompression, the tolerance increases, sometimes quite rapidly [Hiestand & Stemler (51, 52)]. In whole mice there is no influence on over-all rate of metabolism by acclimation to low oxygen (simulated altitude of from 16,000 to 18,000 ft.) or to 0.14 per cent CO in air [Clark & Otis (53)]. In albino rats acclimated to chronic hypoxia the oxygen uptake of brain, diaphragm, liver, skeletal muscle, and heart remained unchanged, adrenal Q_{O_2} increased, kidney Q_{O_2} decreased [Ullrick & Whitehorn (54)]. The chemistry of rat brain, including cytochrome oxidase, is unaffected by acclimation to simulated altitudes between 11,000 and 18,000 ft. but 3 min. in nitrogen results in reduced high-energy phosphate bonds and increased lactic acid and inorganic phosphate [Albaum & Chinn (55)].

Deleterious effects of high oxygen pressure.—In rabbits prolonged breathing of pure oxygen at 1 atm. causes death by asphyxia which results from damage to the pulmonary epithelium. Abdominal pCO_2 is increased 15 mm. Hg above normal during the first 12 to 15 minutes of breathing oxygen at 7 atm., then it rises sharply, presumably because fixed acids accumulate. Damage to enzyme systems is indicated [Bahnson & Matthews (56); cf. also Lambertsen *et al.* (57)]. In cats inhaling oxygen at 6 atm. the brain pH drops from 0.25 to 0.53 pH in 30 min., followed by convulsions and death [Perot, Stein & Sonnenschein (58, 59)]. In man, central accumulation of CO_2 on oxygen breathing at 3.5 atm. does not contribute to the toxicity of oxygen [Lambertsen *et al.* 60)]. In rats, hypophysectomy offers some protection, on central nervous system and on lung parenchyma, against toxicity of oxygen at high pressure. The protection is partially abolished by ACTH[2] [Bean (61), Bean & Johnson (62)]. Guinea pigs show some adaptation when repeatedly subjected to hyperpressure [Frada, Cali & Romano (63)]. Lück studied

growth as a function of oxygen pressure (air with 0 to 7 atm. excess oxygen pressure) in 13 species of bacteria, yeast, *Aspergillus*, and *Penicillium*. There is progressive inhibition, complete at different oxygen pressures depending on the organism used (64). In *Escherichia coli* no inhibition (by 8 atm. excess oxygen pressure) of alkaline phosphatase and proteinase is observed. Catalase activity is increased. Dehydrogenases are irreversibly inhibited in the course of 1 hr. (38°C.) at excess oxygen pressures exceeding 3 atm. At 8 atm. the inhibition is 40 to 50 per cent. The lactic acid production of *Lactobacillus casei* diminishes even at low excess oxygen pressures [Lück (65)].

Marine animal plankton, and especially fish fry, avoid places too rich in phytoplankton and hence too high in oxygen content [Dannevig (66)]. Pond and sea organisms adapted to waters containing oxygen in amounts less than that corresponding to saturation with air die sooner when the water is saturated with air [Fox & Taylor (67)].

Mechanics, Respiratory Reflexes

The water beetle *Hydrous piceus* shows absence of ventilation control and the air volume carried on the outside of the body mainly represents an oxygen store which (except at low temperatures) must be frequently refilled at the surface. In *Naucoris cimicoides* and in *Notonecta glauco* the "air store" represents a "physical gill" because it is effectively ventilated by swimming movements and by ventilation with the hind legs [de Ruiter *et al.* (68)]. Technical problems in measuring respiration in such animals were discussed by Wolvekamp & Vlasblom (69), and an apparatus was designed. The function of the "gill" depends on the presence of nitrogen and on the fact that nitrogen is less soluble in water than oxygen is. With the same gradient the amount of oxygen which moves into the gill is greater than the amount of nitrogen which moves out. However, the "gill" continues to get smaller and must occasionally be renewed by visits to the surface. Many insects carry thin layers of air between hydrophobic hairs. Capillary forces lower the total pressure in the air below that in the water, the nitrogen gradient is abolished, and the "plastron" becomes a permanent gill [Thorpe (70)]. The caddis fly *Hydropsyche angustipennis* dives vertically into the water when eggs are deposited and stays submerged for up to 37 min. Possibly layer of air carried down on the hairy body acts as a physical gill [Badcock (71)]. The aquatic beetle *Potamyces tuberosus* is surrounded by an impressive air bubble, acting as a physical gill. The animal inhabits streams with rapid flow. As observed by Stride (72) the flowing water produces underpressure in the bubble; consequently the nitrogen gradient is abolished or even reversed. The "gill" becomes permanent because the beetle settles only where the stream is rapid enough. Surface forces in the tracheal system of insects were discussed by Wigglesworth (73). The air extends into the tracheoles gradually as available oxygen decreases from 100, to 21, 10, 5, and 1 per cent oxygen. The opening and closing of the spiracles also depends upon the oxygen tension. Wigglesworth interprets the evidence in support of his view that acid metabolites

accumulate when the oxygen pressure drops, and he states that there is a different equilibrium in the metabolism of the tissues at each partial pressure of oxygen. Direct regulation on oxygen concentration in the tissues was not excluded. In the bug *Rhodnius* tracheoles migrate towards places of minimum oxygen tension, and low oxygen tension induces active outgrowth of tracheae and tracheoles [Wigglesworth (74)]. The gnat *Aedes aegypti* has olfactory receptors for carbon dioxide on the first flagellar segments of the antennae of both sexes [Willis & Roth (75)]. Waterman & Travis report on respiratory reflexes and flabellum in *Limulus* (76). Wells & Dales (77) traced and discussed the irrigation pattern of the marine worms *Nereis diversicolor* and *Chaetopterus variopedatus*. Marneffe-Foulon (78) describes phases in the pulmonary respiration of the frog. In the trench the utilization of oxygen from the water flowing over the gills drops from 51 per cent when blood and water flow in opposite directions (normal condition) to 9 per cent when the flow is parallel [Hazelhoff & Evenhuis (79)]. Sturkie reviews respiration and energy metabolism of birds (80).

The Oxygen Gradient

Hemoglobin was demonstrated in parasitic cirripede crustacea by Fox (81), but its respiratory significance remains obscure. In *Serpula* chlorocruocin and hemoglobin (hb) are both present, and they have identical affinities to oxygen (82). In *Daphnia* hb^2 is present under conditions of anoxic stress, and it disappears when oxygen in the water increases. It has a respiratory function not only in the parthenogenetic eggs which pick it up and show increased rate of development but also in the animal itself. Pale individuals die sooner than red ones in low oxygen. In water containing less and less oxygen they feed progressively less, and normal animals feed more than CO-treated ones and also they produce more eggs [Fox, Gilchrist & Phear (83, 84)]. The snail *Australorbis* (carries hb) when infected with *Schistosoma* produces fewer cercariae the lower the oxygen of the environment [Olivier, von Brand & Mehlman (85)]. In *Daphnia* hb synthesis is favored by high temperature probably via low tissue oxygen [Fox (86)]. It is stimulated by factors present in duck faeces polluting natural waters, it is slightly stimulated by vitamin B_{12} added to the water and much by ferrous salts [Fox, Phear & Gilchrist (87), Fox & Phear (88)]. In *Planorbis* low concentrations of CO inhibit respiration somewhat when O_2 (in moist air) is below 5 per cent. In *Limnea* there is an expressed inhibition at all tensions studied. Since *Limnea* carries hemocyanin in its blood, Füsser & Krüger (31) hold tisssue hemins responsible; for this, proof is lacking. The results should perhaps be taken as a warning against too much generalization with regard to affinities from a few known cases, especially when the CO/O_2 ratio is ill-defined. CO treatment which in hemoglobin-containing species blocks hemoglobin and produces asphyxia [Walshe (89)], does not affect hemoglobinless species of chironomids. In Koenen's (32) small oligochetes blocking of the hemoglobin by CO reduces the respiratory rate at all oxygen tensions from 380 mm. Hg

to near zero. For the chironomid larvae it has been pointed out by Prosser (2) that a steep oxygen gradient exists between the environment and the sites of unloading of the hemoglobin.

For *Chironomus plumosus flaveolus* Walshe observed that filter feeding ceases below 10 per cent air saturation but below 26 per cent in the presence of CO. Among four leaf-mining species inhabiting glass tubes Walshe (89) found that the filter feeding of the two red ones (*Glyptotendipes pallens* and *Endochironomus dispar*) is reduced at low oxygen concentrations if the hemoglobin is first rendered functionless by CO. The animals use correspondingly more time for respiratory irrigation. The pale species (*E. tendens* and *E. albipennis*) was uninfluenced by CO. It is puzzling that the pale species showed more (90 per cent) filter feeding and less irrigation activity than the red ones (60 per cent) at all oxygen concentrations, and one (*E. tendens*) continue unchanged filter feeding down to 10 per cent air saturation. Absence or presence of hb may one day be observed to represent adaptations to tissue oxygen concentrations as it is known for *Daphnia* (86). The oxygen independent behavior of the two pale species might reflect relatively high tissue tensions and small oxygen gradients which cannot be referred to exceptional energetic respiratory ventilation. The oxygen permeability of the integument might be higher than in the red species. In *C. plumosus flaveolus* maximum respiratory regulation, i.e., continuous irrigation, is at 5 per cent air saturation as contrasted to 10 per cent in *C. plumosus plumosus*[Walshe-Maetz (15)]. Adapted in its tube *C. plumosus plumosus* is independent of changes in oxygen down to 45 per cent air saturation. Below this tension larvae with a functional hemoglobin are less dependent than larvae in which the hemoglobin is blocked with CO. However, the respiratory behavior, especially of *C. plumosus flaveolus*, suggests that hb functions at all normal environmental oxygen tensions, loading during irrigation and de-loading in between. Between 45 and 10 per cent saturation with air Q_{O_2} drops 30 per cent, and in the interval (biological for this species) the animal compromises between necessity for feeding and for respiration. Muscular (ventilation) activity increases when pO_2 decreases, so presumably the respiration decreases sharply in tissues other than the muscles. Compensatory changes in the anaerobic metabolism are possible, but the animals' feeding economy would be better served without them. For animals which circulate the hemoglobin, the transport and storage functions can never be separated because O_2 is stored during the transport and perhaps longer. The relative significance of the two functions of hb is discussed by Walshe-Maetz (15) for the chironomids. Decision must await a simultaneous study of the circulation. The marine worm *Nereis virens* is another tube-dweller which shows intermittent irrigation. In the irrigation phase blood is circulated through the skin, but in resting periods oxygenated blood is shifted for storage in central blood vessels [Lindroth (90)]. In *Nereis* (cf. Walshe-Maetz for *C. flaveolus*) the oxygen depot is too small to cover more than half of the demands in the resting periods. However, oxygen demands are not easily defined. They might de-

pend on tissue oxygen tensions. Hemoglobin is present in yeasts, where it may function in respiration under certain conditions [Keilin (91)], in *Neurospora crassa*, *Penicillium notatum* [Keilin & Tissières (92)], and with other hemoproteins, in the ciliate protozoon *Tetrahymena pyriformis* (Keilin & Ryley (93)]. A strain (W) of *Tetrahymena* accumulates protoporphyrins [Rudzinska & Granick (94)]. For mammalian muscles from different sources there is close correlation between concentration of enzymes of the oxidative cycle and myoglobin present [Lawrie (95)]. Prolonged enforced muscular activity stimulates myoglobin synthesis [Lawrie (96)].

Alone among vertebrates, five antarctic species of fishes have colorless blood [Ruud (97)]. In *Chaenocephalus aceratus*, microscopical observations were supplemented with determinations of oxygen capacity and of blood iron to confirm absence of hemoglobin. *C. aceratus* is a sluggish fish, sometimes weighing more than 1 kg., and presumably it is restricted to well aerated water of less than 2°C. Fox (see 97) comments that many fishes tolerate CO in concentrations which block the hemoglobin, but they then lack the ability for increased activity. Brain breis from active species of fish respire at about double rate compared to breis from sluggish fishes [Vernberg & Gray (98)].

Activity

Rhythms.—The oxygen uptake of the fiddler crab (*Uca pugilator*) is high at night and low ($\frac{1}{2}$ to $\frac{1}{4}$) in the daytime. The 24 hr. cycle corresponds closely to the cycle of activity. Eyestalk removal increases oxygen uptake, bilateral more than unilateral, and eyestalk extract or implanted eyestalk tissue counteracts the metabolic and other effects of the operation. DDT imitates the eyestalk hormone and both are believed to exert primary action on tissue calcium [Edwards (99)]. In the periwinkle (*Littorina littorea*) and in the oyster drill (*Urosalpinx cinereus*) Sandeen, Stephens & Brown (100) observed diurnal metabolic rhythms. In *Uca pugnax* a persistent tidal rhythm is superimposed [Brown, Bennett & Webb (101)]. In the wood louse (*Oniscus asellus*) the sensitivity of CO_2 shows diurnal variations [Cloudsley-Thompson (102)]. The amplitude of the daily metabolic variations in white mice are about the same at all temperatures from $-8°$ to $+37°$C. The resting metabolism (lowest values in daytime) at $-8°$C. is five times that at $+32°$C. At all temperatures, metabolism of work is superimposed upon that of rest. This results in very large energy expenditure at low temperatures [Hart (103)]. The site of energy release during work and in response to cold is different [Hart & Heroux (104)]. The diurnal metabolic rhythm in white mice (10°, 20°, 30°C.) results from a rhythm in voluntary muscular activity, disappearing when constant work levels are imposed in a tread-mill apparatus [Hart (105)]. The daily voluntary activity was calculated to average 12, 16 and 27 per cent of the daily expenditure at 10°, 20° and 30°C., respectively (105). Hart (106 to 111, 113) and Hart & Heroux (112) have published further interesting papers on metabolism, body temperature, temperature acclimation, humidity, and body insulation in mice. They should be con-

sidered together with the important papers by Scholander and co-workers (114, 115, 116) and by Sullivan & Mullen (117) on adaptation to cold, body insulation, basal metabolic rate, and heat regulation in arctic and tropical birds and mammals.

Metabolism during flight.—Krogh & Weis-Fogh (118) induced the desert locust (*Schistocerca gregaria*) to continued tethered flight performance in a small chamber by stimulating it with a jet of air hitting an aerodynamic sense organ on the upper part of the head. The oxygen uptake is circa 15 l. O_2/kg./hr. or 20 to 25 times the resting value. A small oxygen debt is contracted and is repaid after ½ to 1 hr. of rest. R.Q. was 0.82 during the first 30 min. of flight and decreased to 0.75 during the succeeding hour. Direct chemical analyses [Weis-Fogh (119)] of animals flying in a roundabout [Krogh & Weis-Fogh (120)] revealed that 80 per cent of the energy liberated was derived from fat. The average oxygen uptake was 16 l. O_2/kg./hr., outer limits 10 and 20 l. The consumption varies with the square of the flying speed but is independent of the outside temperature in the range 25° to 35°C. Flying hummingbirds [Pearson (121)] consume 80 l. O_2/kg./hr. Like Weis-Fogh, Pearson discusses the results in relation to flying distances observed in migrations. Studies of R.Q. in butterflies [Zebbe (122, 123)] suggest that carbohydrate consumed is converted to fat before combustion in the muscles.

Respiration and Body Size

Intraspecific comparisons.—The oxygen uptake varies with the body surface in the earthworm, *Eisenia foetida* [Krüger, at 15°C. (124)], and in three species of prosobranch snails (*Lithoglyphes naticoides*, *Paludina fasciata*, and *P. vivipara*) studied at 23°C. by Krywienczyk (125). For four pulmonate snails (*Planorbis carinatus*, *P. corneus*, *Limnaea auricularia*, *Isodora proteus*, 23°C.) the same author (126) found respiration proportional to a power of the body length (d) intermediary between 2 and 3. For *Limnaea stagnalis* and for *Planorbis corneus* at 14° to 15°C. Füsser & Krüger (31) were unable safely to distinguish between weight and surface dependency of the oxygen consumption. In *Dreissensia*, a fresh-water mussel studied at 23°C. by Ludwig & Krywienczyk (127), the respiration varies with the surface. Will (128) studied three isopod crustaceans, one aquatic (*Assellus aquatica*) and two terrestrial (*Oniscus asellus*, *Porcellio scaber*), and the cockroach *Periplaneta orientalis* (23°C.). She summarizes the situation as viewed by the Heidelberg group (124 to 128): In animals which respire with gills (bivalves, prosobranch snails, *Asellus*) the respiration is proportional to body surface (d^2) but in insects, in some aquatic, and in all terrestric pulmonate snails it varies with body weight (d^3). In *Porcellio*, which has gills and tracheae, the situation is intermediate. There is no reference to the disturbing fact that von Brand, Nolan & Mann (129) found the respiration to obey the surface law, intra- and interspecifically for nine species of pulmonate and eight species of operculate snails (30°C.). Berg (14) found identical rates of oxygen

consumption for two species of fresh water snails (16°C.) when animals of the same size were compared. In the smallest species (*Acroloxus lacustris*) the respiration varied with the 0.69 power of the (soft) body weight (W), and in the larger *Ancylus fluviatilis* with $W^{0.84}$. In the lobster Thomas' results (34) suggest respiration to vary with $W^{0.67}$. Von Bertalanffy & Krywienczyk (130) related the logarithms of the oxygen consumed to the logarithms of the body length for the brine shrimp *Artemia salina*. Presupposing unchanged body proportions from nauplius to adult the slope of the straight-line curve suggests respiration in proportion to the body surface. For the same animal Eliassen (131) obtained very different results. His results were plotted as O_2 body-N/hr. against log body-N, and as log consumption against log body-N. In one series Eliassen observed the rate/body-N curve in the log-log grid to slope with a regression line of 0.75 in the range from 0.1 to 1 μg. body-N. Then, in the range from 1 to 25 μg. body-N the slope was 1.0, and, finally, in the range from 25 to 300 μg. body-N it was 0.6. Thus, for the whole development from nauplius to adult the curve was clearly triphasic. Such a curve was previously observed by Zeuthen (12) for the mussel *Mytilus edulis*, developing from gastrula to adult (O_2/body-N against body-N). Data for the marine prosobranch snails *Nassa reticulata* and *Littorina littorea* (12) had been fitted better with triphasic curves than with the smooth ones presented. Data for *M. edulis*, *Asterias rubens*, *Artemia salina*, *Bufo* and *Rana* together, and for the rat, were plotted log O_2 against log body-weight or -N [Zeuthen (132)]. All curves were discontinuous, probably triphasic. For *Artemia* (131) the curve was subject to some modification by environmental factors such as salinity and season. Striking discontinuities on the curve relating oxygen consumption with size were also observed for the marine nematode *Pontonema vulgare* by Nielsen (133). For sexually immature *Pontonema* (50→150 μg.) the data suggest[2] a $W^{0.4}$ relationship. For sexually mature worms, increase in weight (150→550 μg.) and in O_2 consumption were proportional. For the larger soil oligochete *Mesenchytraeus albidus* Nielsen's data suggest a switch from an exponent (b) 0.5 for growing, immature animals to nearly 1.0 in growing, mature individuals. Using Edwards' data it was observed (132) that in the growth of the crab *Emerita talpoida* b varies from 1.0 through 0 and to negative values indicating decrease in total consumption with continued increase in body weight. Usually (132), but not always (133), minimum values[3] of b were studied for animals over a rather short size range near the maximum size of the species. Vernberg's data (134) for two salamanders (*Plethodon cinereus* and *Eurycea bislineata*) fit here. With weight increasing from 0.55 gm. to 1.45 gm. the total consumption remains nearly constant at 1°C., and thus there is W^0-relationship. At 10°C. the respiration varies more closely with $W^{0.3}$. In the course of their ontogenetic development the species pass through successive stages characterized by regularly changing values of b. There are thus many more "metabolic types" which should be related to phenomena of growth than the three (surface, weight, or in-between) suggested by von Bertalanffy (135). Any single value of b recorded

over a relatively narrow range of body sizes only represents a tangent at one point of a much wider and more complicated curve. The relative abundance in the records for rate/weight studies of regression lines with slopes ranging from 1.0 to 0.76 reflect that most organisms were studied in comparable physiological states, i.e., as sexually mature adults. Even then, b ranges from less than 0 to 1, but probably not above 1, in conformity with thermodynamic considerations by Prigogine & Wiame (136), von Bertalanffy (137), and Spanner (138).

Interspecific comparisons.—For arctic and (separately) tropical birds and mammals data for oxygen consumption/body weight were published by Scholander *et al.* (114). They confirm earlier reports. For arctic and tropical fishes, and for crustaceans (weight from 3 mg. to 150 gm.) the regression line had a slope of 0.85 as demonstrated by Scholander and others (115). In the warmblooded animals and in terrestrial invertebrates the metabolic rate appears to be inadaptive as to climate; in marine fishes and crustaceans it is adaptive. Raymont & Gauld (139, 140) related respiration and body length in three species of planktonic copepods (1 to 5 mm. long). The results check with those just reported. Nielsen (133) for small nematodes from the soil and from the sea [2×10^{-4} mg. (*Monhystera vulgaris*) to 0.4 mg. (*Pontonema vulgare*)] found rates decreasing slightly with increasing sizes [($b=0.9$ (132)]. Three species of protozoa (the ciliates *Bresslaua sp.* and *Paramaecium caudatum*, and the amoeba *Chaos chaos*) together representing a thousandfold volume variation, were compared by Scholander, Claff & Sveinsson (141). The regression of respiration with volume was considerable, with a slope of 0.55. Hemmingsen (142), summarizing data from the literature, observed linear relationship between the logarithm of the standard (basal) metabolism and the logarithm of the body weight for homoiotherms, beech trees, and poikilotherms larger than 0.1 to 1.0 mg., and a proportionality between respiration and $W^{0.73}$ is always observed. Below 0.1 to 1 mg., down to and including bacteria, the metabolism is more nearly proportional to the weight. Zeuthen (132) found that for poikilothermic animals smaller than around 50 mg. (the limit is not sharp, and it is lower for crustaceans) and down to weights corresponding to those of small marine eggs (10^{-3} mg.), the exponent b is 0.95, and in this whole range the metabolic rate (O_2/N) decreases only about 50 per cent with increase in size. Scattered data [(132), cf. also (141)] for bacteria, flagellates, ciliates, and large amoebae collected from the literature suggest low values of b (about 0.7) in the unicellular range from bacteria to the one- to ten-million-times larger amoeba. Bacteria consume 100 to 500 l. O_2 per kg. per hr., amoeba only 0.2. Thus, organisms, together roughly representing the organic world, demonstrate a triphasic consumption/weight curve which the intraspecific curve for several species resembles. In some species or systematic groups the middle phase of moderate regression of metabolic rate with size is long extended. Large bodies with relatively high metabolic rate, as observed in the homoiotherms, result.

Tissue metabolism.—Fried & Tipton (143) for mouse, rat, and cow (brain,

heart, kidney, liver) found inverse correlation between succinooxidase, malic dehydrogenase activities and body size. Intraspecific comparisons revealed no difference. Krebs (144) measured Q_{O_2} of brain and kidney cortex, of liver, spleen, and lung in nine mammals varying in size from mouse to horse. Slices were studied in three new suspension media, at 40°C. Q_{O_2} of tissues from larger animals were somewhat lower than homologous values for smaller species, but no strict parallelism between Q_{O_2} values and basal heat production of the intact animal was found. Krebs suggests "that there is at least one major tissue whose 'basal' Q_{O_2} changes with the body weight approximately with the basal heat production; that this organ is the striated musculature." This suggestion is exactly the opposite of older views of Kestner and of Blank that the relative size of organs of high and low activity gives a complete explanation of the different heights of metabolism in the different animals. Krebs did not study muscles, but von Bertalanffy & Pirozynski (145, 146) studied muscles of rats (37°C.) ranging from newborn to adults and found the diaphragm (heart, lungs, liver, kidney, and thymus were also studied) to be the only organ in which the Q_{O_2} decreased considerably and consistently with increase in size. Skeletal muscles [von Bertalanffy & Estwick (147)] showed slight decreases only. This is said to be a "blow to the hypothesis that the decrease of basal metabolic rate is due to cellular factors" [von Bertalanffy & Pirozynski (145); discussion by Schmidt-Nielsen (148)], and the authors suggest "that the decline in basal metabolic rate depends on regulative factors lying in the organism as a whole" (146). The fact that tissue summation in the case of the 10 gm. rat accounts for only 35 per cent of the respiration of the intact animal is mentioned in support of this view. Many will not like this argument since they consider that the summation represents the only check on the methods employed. Tissue slices suspended in air or in oil show higher and more stable respiration than those in conventional suspension media [Rodnight & McIlwain (149)]. Vernberg (150) studying fish brain, muscle, and liver could demonstrate no statistically significant regression of Q_{O_2} with size. In mammals, intra- and interspecifically, the brain, heart, lungs, liver, and kidneys show negative allometry, i.e., they constitute a smaller and smaller fraction of the body mass as the bodies become bigger [von Bertalanffy & Pirozynski (151)]. Thus, with increase in size the total resting metabolism is indeed partially switched to metabolically less (probably on an average much less) active organs such as bones, connective tissue, and striated muscle. The same slope for the regression line metabolism/weight for a single or for a number of dominating organ(s) (Krebs) as for whole animals is, therefore, not to be expected. The present experimental situation suggests that the regression lines for all organs slope less than those for the whole animals, and this makes sense. For the homoiothermic animals the future is likely to see a compromise between opposing extreme views as those of Kestner-Blank and of Krebs.

The Q_{O_2} of big mammals and reptiles is 0.1 to 1 per cent of that of bacteria and flagellates (132). Thus, the regression of Q_{O_2} values with size is a

basic biological phenomenon exhibited in living beings representing all levels of organization, and it can be resolved only on the cellular level. Protozoa grow by growing bigger cells but metazoa by adding more cells. The steep decline in Q_{O_2} with increase in size in the protozoan range switches to a slight decline in metazoa up to weights of about 50 mg. This suggests that the same functions which operate on the cellular level in the protozoa also operate in determining the metabolic rate in the small metazoa. [Still, Ellenby (152) for diploid and triploid prepupae of *Drosophila* which have different cell sizes failed to demonstrate differences in Q_{O_2}]. It is only after the metazoa grew beyond certain sizes (roughly indicated as 50 mg.) that a new (allometric) function relating body mass and metabolism arose. The vast majority of authors have limited themselves to a discussion of this the latter function.

R.Q. in Diapausing Insects

Agrell (153, 154) observed very low R.Q.'s (0.1 to 0.3) in two diapausing butterflies (pupa of *Phalera bucephala, Endromis versicolosa*). The increase in R.Q. with a fall in temperature is accompanied by a decline in Q_{O_2}. Injection of aneurin resulted in increases in oxygen uptake and in R.Q. Pantothenic acid or saline increased oxygen uptake to some extent, but the R.Q. remained low. Punt (155) demonstrated rhythmic expulsion of CO_2 in a number of insects. Metabolic rate and time between successive outbursts of CO_2 are inversely correlated. In diapausing pupae of the Cecropia silkworm (*Platysamia cecropia*). Schneiderman & Williams (156) observed oxygen uptake to continue unchanged during the time outbursts of carbon dioxide were found to occur. The R.Q. recorded in long term experiments was normal (0.78). Spiracular control of breathing can hardly explain these results. Rather, decarboxylases and terminal oxidases are out of gear. Agrell suggested that decarboxylating steps of the Krebs cycle are partially blocked during diapause. Others (156) seem to find similar blocking, however, with compensatory periodic bursts of decarboxylation.

Terminal Oxidases

The spadix of the plant Arum [review on terminal oxidases in plants by James (157)] shows extremely oxygen dependent respiration, and it respires faster than any other tissue from higher plants. It seems to be entirely devoid of metallo-oxidases. Auto-oxidable flavoproteins are the only terminal oxidases. Extreme, low oxygen affinity is accepted as being typical of flavoproteins. According to Moulder (158) cyanide insensitive species of *Trypanosoma* consume oxygen at a faster rate than cyanide sensitives. In killer *Paramoecium* the presence of the cytoplasmic particle, kappa, is associated with an oxidative system different from the cytochrome system [Simonsen & Wagtendonk (159)]. In air-saturated water, dependent species of chironomid larvae have a higher rate of metabolism than have independent species (16). Bueding & Charms (160) found no cytochrome or cytochrome oxidase in

Ascaris and in *Litomosoides*, and very little in the schistosomes. Respiration (dependent) was suggested predominantly, or exclusively, to be mediated by respiratory catalysts (flavines?) other than the cytochrome system.

Pupae of the Cecropia silkworm are independent of oxygen above 0.05 atm., but only the muscles depend on cytochrome oxidase as a terminal catalyst. The diapause is brought to an end by the secretion of a hormone and (as a result ?) the cytochrome oxidase becomes the principal terminal oxidase in all tissues [Schneiderman & Williams (161)], including spermatogenic tissue studied *in vitro* [Schneiderman, Ketchel & Williams (162)]. Schneiderman & Williams (163) observed light-reversible inhibition of development and killing by carbon monoxide of growing and metamorphosing Cecropias. Only the diapausing pupa is viable in carbon monoxide, but the termination of the diapause is retarded.

The respiration of diapausing Cecropia is only 1.4 per cent of that of the mature larva [Schneiderman & Williams (164)]. This low respiration is stimulated up to fourteen-fold by injury [(164); cf. also Agrell (154) and Sussmann (165)]. The increase is not linked to morphogenetic processes (164), is uninhibited by carbon monoxide (161) and by phenylthiourea (164), and is thus mediated neither by cytochrome oxidase nor by tyrosinase. It returns to normal level only after months (164). Sussmann (165) could exclude tyrosinase as a terminal oxidase in Cecropia. Flavoprotein catalysis in diapause is possible and likely [Shappirio & Williams (166), Schneiderman & Williams (167), Chefurka & Williams (168), and Sanborn (169)]. In yearling rainbow trout, cyanide inhibition of development can be partially overcome by increasing the oxygen tension, suggesting the presence of terminal catalysts which compete with cytochrome oxidase [Downing (170)]. In the metamorphosing and diapausing beetle *Popilia japonica*, Ludwig (171) found cytochrome oxidase activity to parallel variations in O_2-uptake.

In the myxomycete *Physarum polycephala* [Allen & Price (172), Holter & Pollock (173)], in the amoeba *C. chaos* [Andresen, Engel & Holter (174)], and in the ciliate *Tetrahymena geleii* [Ryley (175)] cytochrome oxidase could not be demonstrated, but Seaman (176) found cytochrome oxidase in four strains of *Tetrahymena*. The homogenates were prepared in four different ways, and Ryley's negative findings are referred to loss of activity in the preparations. *Tetrahymena* is independent of oxygen tension (1). Among helminths *Ascaris* survives relatively long in anaerobiosis. For *Ascaris* muscle Chin & Bueding (177) demonstrated anaerobic and aerobic phosphorylation.

Cytochrome oxidase is present in starfish sperm [Borei & Metz (178)]. Cytochromes *b*, *c*, *a*, and a_3 were demonstrated in the housefly *Musca domestica* by Sacktor (179), and a new cytochrome (*x*), was observed in the Cecropia silkworm by Sanborn & Williams (180).

Carbon monoxide compounds of cytochrome oxidases were intensively studied by Chance (181); heart muscle uses cytochrome oxidase [Chance (182)]. Terminal oxidases in bacteria are reviewed by Ajl (183).

Longmuir (184) produces strong evidence that the terminal oxidases in nine species of bacteria in baker's yeast and in mitochondrial enzyme preparations from ox and pig heart are saturated with oxygen at exceedingly low (fractions of a mm. Hg) oxygen tensions. Rate of decrease of oxygen tension was followed polarometrically in suspensions, and the shape of the curves appear similar to substrate concentration × time curves for enzymatic reactions. It was conceived that a bacterium stands in the same relationship to oxygen as an enzyme to its substrate, and the concentration of oxygen at which the bacterium respires at half maximum rate was designated *Km* (Michaelis constant). *Km* plotted against the diameter (0.6 to 4 μ) of the bacteria suggests measurable diffusion gradients for oxygen even in these small cells. Longmuir & Roughton (185) measured diffusion constants for carbon monoxide and nitrogen in hemoglobin solutions. In 30 to 40 per cent hb (that of the red cells) D_{N_2} is 0.2 to 0.3 of that in water.

Methods

Cartesian diver methods for respiration measurements were published by Zeuthen (186, 187) and by Scholander, Claff & Sveinsson (188). The methods (187, 188) are for single cells in the range of small marine eggs and of ciliates. The device (187) permits work under sterile conditions (188) as well as measurement shortly after loading. Capillary respirometers are discussed by Gregg (189, 190), modifications by Brachet (191). Prop (192) combined a capillary microrespirometer with a device for measuring CO_2 by conductivity of Ba $(OH)_2$, and Tuft (193) equipped a microrespirometer with devices for automatic setting and recording. Discussion of special aspects of manometric and volumetric methods was given by Kok, Veltkamp & Gelderman (194). Danes, Christiansen & Leinfelder (195) combined the Cartesian diver microbalance for determination of submerged weight (*RW*) of live cells or tissues with a capillary respirometer for studies on tissue cultures. *RW* was used as a reference in respiration studies by Holter & Zeuthen [cf. Holter (196)]. Deoxyribonucleic acid [Davidson & Leslie (197, 198); Jacob, Mandel & Mandel (199)] and nuclear counts [Sanford *et al.* (200)] are other accepted references.

Lucite microvolumetric respirometers for small invertebrates and tissues were discribed by Wennesland (201) and by Scholander and co-workers (202). Schneiderman & Feder (203) developed a respirometer for work with insect pupae at high pressures (for easy establishment of high CO/O_2 ratios). Benzinger & Kitzinger (204) report on a microcalorimetric method for simple biochemical systems. Oxygen tension [Penneys (205)] and oxygen consumption [Bartels & Moritzen (206)] of skin, and of yeast and bacterial suspensions [Ewald & Bruchmann (207); Longmuir (184)] was followed with polarographic methods. These methods, now widely used, are discussed in Tödt *et al.* (208). Flow respirometers using the oxygen cathode, adapted for work with nerve, were published by Carlson, Brink & Bronk (209) and by Conelly, Bronk & Brink (210).

Conclusions

Oxygen-dependent respiration seems to be more common than oxygen-independent respiration. There are cases of considerable tolerance (absence of regulation) to impressive changes in rate of respiration induced by variations in oxygen tension. R.Q. in snails suggests that in response to moderately lowered oxygen there are no compensatory changes in the anaerobic metabolism. "Independent" versus "dependent" respiration is often discussed in terms of diffusion of oxygen as a limiting factor, but many observations do not fit this picture, and tissue respiration is sometimes dependent. Other factors which determine the intensity of the respiratory metabolism at different oxygen pressures may be the affinity of terminal respiratory catalysts to oxygen. In animals only cytochrome oxidase and flavoproteins have been seriously proposed. The former enzymes have high, the latter low, affinity to oxygen. There are observations to suggest that the energy yield is lower in complete anaerobiosis than in aerobiosis, and sometimes much lower. Oxygen debts are difficult to measure and to evaluate. However, in some cases evidence is good that the energy deficit accumulated in anaerobiosis is not made good in postanaerobiosis. Thus, within wide limits oxygen tension seems to exert a regulatory function on the energy turnover of animals. This regulation is likely to be not only in the degree of saturation of terminal oxidases, but also in redox equilibria higher up in the oxidative or glycolytic chain. It follows that many animals have it in their power to regulate within limits their energy metabolism ("rate of living") by exerting respiratory control. This control may be against too low oxygen, but also against too high an oxygen tension. In some cases air represents too high an oxygen tension. The "maintenance metabolism" may to a considerable extent serve to repair damage resulting from auto-oxidations in living systems. According to this view "dependent" respiration shows that the extent of auto-oxidative damage increases with the oxygen pressure in the tissues. "Independent" species should be less sensitive to high oxygen pressure than are "dependent" species, and the difference between the two categories should be quantitative, rather than qualitative. No report relating turnover of tissue components and oxygen tension was encountered, but reduced rates of growth at low oxygen tensions were reported.

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COMPARATIVE PHYSIOLOGY: NUTRITION, FEEDING, AND DIGESTION[1]

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This review summarizes the results obtained in approximately the last five years. For comparison with the results of literature before 1949 the works of Prosser (1), Scheer (2), Heilbrunn (3), Bourne & Kidder (4), and Buchner (5) may be consulted. The literature on nutrition is arranged according to the problems; the rather divergent works on feeding and digestion are arranged according to the systematic groups. In general the literature has been reviewed up to January 1954; papers of more recent date could only be considered occasionally. Because this review was composed at a considerable distance from the large centres of scientific research, completeness is not claimed.

Nutrition

Requirements of amino acids.—About 1949 the amino acid requirements of three invertebrates were fairly adequately known, viz. of *Tetrahymena geleii* (*Glaucoma pyriformis*), *Aëdes egyptae* (12) and *Attagenes* sp. (13). Since then our knowledge in this field has been enriched by results obtained from experiments with three other animals, all insects, viz. *Drosophila*, the honey-bee, and *Calliphora*. These results, together with those for *Tetrahymena* are compiled in Table I. Some additions to the data of this table may follow here.

Based on their results of 1945 (6), Kidder & Dewey (7) developed a "complete medium" for the culture of *Tetrahymena geleii* strain W. Contrary to data in Prosser's (1) Table 21, they now (7) consider serine as essential and glycine as nonessential. Elliott (8) came the same conclusion for *Tetrahymena geleii* strain E.

Culture variations of *Tetrahymena* in response to changes in the amino acid concentrations of the synthetic media have been studied by Dewey *et al.* (9), and by Elliott & Hogg (11). If certain essential amino acids are lacking, adaptation may be possible, which shows itself by a renewed growth and increase in population after a certain period of inactivity. The results indicated in Table I for *Drosophila* (14) are based on the fact that the 13 amino acids indicated as essential were adequate for growth. Experiments in which each one of the components is omitted in turn have not been performed.

[1] The following abbreviations have been used in this chapter: RNA (ribonucleic acid); DNA (desoxyribonucleic acid).

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TABLE I

AMINO ACID REQUIREMENTS*

	I	II†	III	IV
Glycine	−	+	−	−
Alanine	−	−	−	−
Valine	+	+	+	+
Leucine	+	+	+	+
Isoleucine	+	+	+	+
Serine	+	−	−	−
Cystine	−	+	−	−
Methionine	+	+	+	+
Threonine	+	+	+	+
Arginine	+	+	+	+
Lysine	+	+	+	+
Aspartic Acid	−	−	−	−
Glutamic Acid	−	+	−	−
Phenylalanine	+	+	+	+
Tyrosine	−	−	−	−
Tryptophan	+	+	+	+
Histidine	+	+	+	+
Proline	−	−	−	−
Hydroxyproline	−	−	−	−

* + essential; − nonessential; I *Tetrahymena geleii*, strain W and E (6, 7, 8, 10); II *Drosophila melanogaster*, strain Oregon R (14); III *Apis mellifica, L* (15); IV *Calliphora erythrocephala* (16).

† Preliminary; not with omission experiments.

These results therefore have a somewhat preliminary character. Beside the ten amino acids which are essential for the rat, glycine, cystine, and glutamic acid seem to be necessary. The authors stress that the results are better when five other acids, viz. alanine, aspartic acid, proline, hydroxyproline, and tyrosine are also present. D-Serine is toxic, and even L-serine seems to be toxic to a certain degree.

An elaborate investigation on the protein and amino acid requirements for the adult state (imago) of the honey bee (*Apis mellifica L.*) has been carried out by De Groot (15). Attempts to rear larvae outside the bee colony have not yet succeeded, the bees could not be reared under aseptic conditions, nor could experiments be carried out with earlier stages. Within three days after emerging, dry weight increases 37.5 per cent, the nitrogen content 36.8 per cent, whereas later on these two figures do not vary appreciably. These increases in the first three days after emergence have been taken as indices for evaluating the significance of the various dietetic compounds. The longevity of the bees may also be used for this purpose. For various reasons [see De Groot (15, p. 243)] the first method has been preferred. The results for

the honey bee given here in Table I show that there is a great similarity between its requirements and the requirements of other invertebrates (and vertebrates) investigated so far. The quantitative requirements of the ten amino acids essential for this animal proved to be highest for leucine, isoleucine, and valine, lowest for tryptophan, histidine, and methionine, and intermediary for arginine, lysine, phenylalanine, and threonine. The amount of these acids in the natural protein sources of the bee, viz. pollen and "royal jelly,"[3] is amply sufficient for the animals' needs. In soybean flour (which has in practice been used without success as a substitute for the natural source of protein) the amount of methionine is short of the amount required.

Of D-amino acids only phenylalanine, methionine, and histidine can be used to some appreciable extent, in the order as mentioned. Feeding of diverse substances which in other animals can be used as substitutes for essential amino acids revealed that the honey bee is more exacting in its requirements than are many other animals, including vertebrates. As in other animals, for the honey bee the stimulating effect which is caused by the addition of nonessential amino acids is also caused by the use of other sources of ammonia-nitrogen.

Growth on diets of amino acids was not far behind that obtained on the natural sources of nitrogen. Contrary to the results of many previous investigations it was found that older bees, too, can consume protein and they may profit by its consumption, a conclusion which may also be of practical interest. The original paper contains much additional interesting detailed information, and gives an excellent review of the literature especially for insects.

The amino acid requirements of *Calliphora erythrocephala* Meigen, have been studied by Sedee (16). The larvae could be reared from the egg aseptically on a semisynthetic diet consisting of casein, cholesterol, salts, cystine, vitamins, and water. In this diet casein can be replaced by its acid hydrolysate, supplemented by tryptophan. If this casein hydrolysate was replaced by a mixture of 17 amino acids based on the composition of casein, growth was poor. By altering the concentrations of the amino acids in this mixture fairly good growth could be obtained. These two media could be used to investigate the significance of the various amino acids for the growth of the larvae. As a criterion for growth the dry weight of the seven-day-old larvae was used. The results (see Table I) demonstrate that *Calliphora* does not deviate appreciably from the normal pattern. Although glycine is not essential, its omission retards and its addition stimulates growth considerably. Hogg & Elliot (17), have investigated the possibility of replacing the amino acids essential for *Tetrahymena* by related components, e.g., by the corresponding keto-acids, as is possible for higher animals. Much similarity between *Tetrahymena* and vertebrates was found in this way, e.g., leucine and

[3] "Royal jelly" is the secretion product of the pharyngeal salivary glands which serves for feeding the larvae and the queen.

phenylalanine can be totally replaced by the corresponding ketoderivatives (α-keto-isocapronate and phenylpyruvate, respectively). Ornithine and citrulline can spare arginine, which suggests the presence of a Krebs-Henseleit cycle in *Tetrahymena*. On the whole, twenty-two points of similarity and four points of difference with vertebrates were found, whereas on two points the results were dubious.

It is certainly astounding that so much similarity exists between the amino acid requirements of organisms so widely different in organisation and systematic position as *Tetrahymena*, insects, birds, and mammals. This indicates that the basic pattern of protein metabolism and synthesis must be the same for these animals. Although growth takes place in the absence of the so-called nonessential amino acids, it has been found that for many of the animals investigated addition of these nonessentials enhances growth, sometimes even considerably. When, moreover, we take into consideration that some amino acids, like arginine, are essential for man during growth and nonessential in the adult state, we are led to believe that at least the concept of nonessential amino acids is rather relative.

TABLE II

VITAMIN REQUIREMENTS*

	I	II	III	IV	V	VI
Cholesterol		+		+	+	
Thiamine	+	+	+	+	+	+
Riboflavin	+†	+	+	+	+	+
Niacin	+	+	+	+	+	+
Pantothenic ac.	+	+	+	+	+	+
Pyridoxine	+	+	+?	+	+	+
Biotin	−	+	+	−	+?	+
Folic acid	+	+	+	−	+?	+
Inositol		−	−	−	−	−?
Choline	−	+	+	+	−	+
p-amino-benzoic acid		−	−			
B_T		+	−	+	−	
Protogen	+		−			
B_{12}	−		+?	−		−?

* + necessary; − not necessary; +? or −? doubtful; blank: not tested; I *Tetrahymena geleii*, strain W and E (7, 10, 21, 21a, 22); II *Tenebrio molitor* (27); III *Drosophila* (14); IV *Palorus ratzeburgi* (28); V *Tribolium confusum* (27, 28); VI *Calliphora erythrocephala* (23).

† For strain *E* doubtful.

Requirements of vitamins.—In addition to the table given by Prosser (1) on the requirements of vitamins by insects (p. 125), Table II of this review provides information on the new facts gathered since 1949. With the excep-

tion of mammals and birds, almost all of the work on vitamin requirements concerns insects and the protozoan *Tetrahymena*. From this table it may be seen that the experience gathered on forms investigated since 1949 has not materially altered the picture given by Prosser. The new factor protogen, isolated by Stokstad and co-workers (18), up to the present has been found to be necessary only for *Tetrahymena*. The factor B_T has recently been found to be identical with carnitine [Carter *et al.* (19)]; by far the largest amounts are found in mammalian skeletal muscle and commercial preparations of meat extracts, less in yeast and wheat [Fraenkel (20)]. Moreover it is remarkable that biotin, necessary for almost all animals, is not required by *Tetrahymena*. The requirements found by Kidder & Dewey (21) for strain W of that organism according to Elliott (22) are the same for strain E (*Colpidium striatum*). In another publication of 1949 Kidder & Dewey (21a) have stressed, that pyridoxine, riboflavin, pantothenic acid, and nicotinic acid are essential for *Tetrahymena*, contrary to the results of their earlier publications.

Inorganic requirements.—These were studied by Kidder, Dewey & Parks (24) for *Tetrahymena geleii* strain W. Older results are considered as untrustworthy because of insufficient purity of the salts used. The basic medium of Dewey *et al.* (9) was used. It was found that potassium, magnesium, and phosphate are absolutely necessary. Omission of potassium reduces growth to one fourth. Lack of phosphate or magnesium stops growth totally. Leaving out calcium, or sulfate, however, has no effect. Iron, copper, zinc, cobalt, fluorine and boron are perhaps necessary in traces; however, it was impossible to prove this. For technical reasons sodium and chloride could not be investigated. Slater (25) has investigated the magnesium requirements of *Tetrahymena*. In agreement with Kidder *et al.* (24) he concludes that magnesium is essential. The amount necessary increases with the concentration of glucose present. This is explained by the role of magnesium as a component of co-enzymes in the dissimilation of glucose. He studied also (26) the necessity of cobalt, which is present in vitamin B_{12}. Previous authors had found that neither B_{12} nor cobalt is essential for *Tetrahymena*. However it is also present in phosphoglucomutase and plays a role in the tricarboxylic acid cycle. With specially purified preparations cobalt was found to be essential. As for magnesium proportionally more cobalt is required when the concentration of glucose in the medium is increased. Evans & Pendleton (26a) found that radioactive phosphate is taken up by *Paramecium* only in the food and not from the surrounding water, whereas *Amoeba* can absorb it directly [Mazia & Hirshfield (26b)].

Nutritional requirements in general, different media.—For some of the animals investigated synthetic media consisting only of amino acids. vitamins, salts, and some source of energy (mostly glucose or acetate) have not yet been devised, although optimal growth was obtained on complex media. Such is the case for *Tenebrio*, the mealworm [Frankel *et al.* (27)] which shows optimal growth on 75 or 80 per cent glucose or starch and 20

per cent casein. With 20 per cent glucose[4] or starch, growth is very slow. With 10 per cent casein, growth is still optimal, but between 5 and 1 per cent casein, a considerable decrease takes place. This diet must be supplemented by the necessary vitamins, according to Table II, including cholesterol or another sterol.

In their paper on *Palorus*, Cooper & Fraenkel (28) found that, with sufficient vitamins, yeast, and salts, growth is optimal on a medium of 80 per cent glucose and 20 per cent casein. However, the decrease in growth if casein is left out is negligible, provided that the other factors are present in optimal amounts. Probably the protein requirements are very small and can be furnished by the protein of the yeast (five per cent) present. For *Blattela orientalis*, the cockroach, Lafon (29) found a minimum protein requirement of 2.5 per cent, the optimum at from 15 to 45 per cent in the diet. Fats can be replaced totally by carbohydrates. Even a diet of pure protein support is tolerated, but the appetite and growth are reduced. If carbohydrate and protein are available, the animal instinctively consumes an amount of protein lying within the wide limits of optimal values.

Paramecium aurelia has been cultivated by Van Wagtendonk & Hacket (30) in a sterile heat stable medium containing equal parts of autoclaved 0.5 per cent yeast autolysate and lettuce infusion in which *Aerobater aerogenes* had grown for 24 hr. and which was then autoclaved. For *P. multimicronucleata* the media described in the older literature are rather complex and contain a heat-stable and a heat-labile fraction of pressed yeast juice. Johnson (31) showed that the heat labile fraction could be replaced by hydrolysed nucleic acid (RNA^1 or DNA^1). The medium consisted of 1 per cent proteose peptone and autoclaved pressed yeast juice (1:20). Per milliliter of medium 100 μg. hydrolyzed DNA was added. The 100 μg. DNA can be substituted by 50 μg. guanylic acid and 50 μg. cytidylic acid. Attempts to substitute the proteose peptone by chemically defined media of amino acids (as Kidder & Dewey's mixture of amino acids and vitamins valid for *Tetrahymena*), or by a hydrolysate of casein, were unsuccessful. Neither could the pressed yeast juice be replaced by a mixture of the known B-vitamins under addition of B_{12} and protogen. Culture in a heat-stable medium is now possible, but the exact requirements of vitamins and amino acids have not yet been determined.

The use of different related organic compounds by *Chilomonas paramecium* has been studied by Cosgrove & Swanson (32). The stock-culture medium contained ethanol as the source of carbon. Only the even numbered straight-chain acids and even numbered straight-chain monovalent alcohols maintained growth comparably to that on acetate or ethanol. Butanol and butyrate even surpass ethanol and acetate as substrates. The somewhat divergent results obtained by Reinhardt (33) (possibility of growth on the lower iso-compounds and odd-number compounds) can perhaps be explained

[4] It is, however, not clear what exactly is meant by 20 per cent glucose, etc.

by the use of a different strain or by the choice of dry weight instead of number of organisms as a criterion for growth.

Chemotrophy of animal organisms.—It has been claimed [Mast & Pace (34)] that *Chilomonas paramecium* is able to grow on a sterile purely inorganic medium, if Si is present. The necessary energy would be derived from an oxydation of some inorganic material, probably NH_3. Other investigators have failed to corroborate such chemotrophy e.g., Cosgrove (35) who found that growth in a solution of analytical pure inorganic chemicals ceases after three days, whereas it is continued much longer if acetate is present. Increase of organic C or CO_2 in the culture could not be demonstrated. The earlier positive results are probably attributable to the use of cotton plugs which give off organic material. To avoid this glass covers must be used. The slight growth which still occurs in inorganic media is attributable to traces of carbon compounds which proved to be present even in analytical pure salts.

For *Astasia longa* strain J, chemoautotrophy had been claimed by Schoenborn. In view of the work of Cosgrove, Schoenborn (36) reinvestigated this question for the flagellates *Astasia longa*, *A. Klebsii* and *Khawkinia quartana*, and a reinvestigation of *Astasia longa* strain J is in progress. These organisms did not grow in the medium found favourable for *A. longa*. Therefore, at present the evidence for chemotrophy of unicellular animal organisms seems extremely weak.

Nutritional conditions in the sea in general.—The production of living matter near Plymouth has been studied extensively by Harvey (37). Armstrong & Atkins (38) reported on the suspended matter in the English Channel. Armstrong & Harvey (39) described the cycle of phosphorus in the Channel and presented evidence that the total amount of phosphorus present is a measure of the potential fertility of the water.

FEEDING AND DIGESTION

Protozoa.—Kitching (40) has described the process of feeding of the suctorian *Podophrya*. Some local external digestion must take place, followed by a suction through the hollow tentacles, for which possible mechanisms are suggested.

Spongifera: sponges.—The feeding and digestion in this group has been studied by van Weel (41) for a tropical fresh water sponge (*Spongilla proliferens* Annand.) and by Kilian (42) for the European fresh water sponge, *Ephydatia fluviatilis*. Their results generally confirm those of the older work of van Trigt (43) and of Pourbaix (44). Van Weel gives a good anatomical introduction, Kilian many good illustrations. Kilian found the flagellae to be considerably longer than was reported earlier by van Trigt. Movements of the flagellae are undulating, never spiral or screw-like as reported by van Trigt. In 24 hr., 1200 times the volume of the flagellated chamber flows through a chamber [equal to from 200 to 300 times the volume of the animal which agrees with Pütter's and van Trigt's results (43)]. Van Weel and Kilian agree that small particles are caught by the outside of the choanocyte

collar, transported (in an unknown manner) to its basis and phagocytized by the cell body. There they are taken up by the wandering phagocytes (archaeocytes) and transported through the whole body. Van Weel saw that the transition from choanocyte to phagocyte takes place by the temporary formation of a small syncytium. Kilian failed to observe this. It is agreed that larger particles are phagocyted in the incurrent canals and in the surface (dermal layer) of the animal. Van Weel described digestion of fat and protein in the phagocytes (globules of milk, blood corpuscles, and spermatozoa). Both authors agree that undigested particles are transported by the phagocytes to the excurrent canals and excreted there. No excretion takes place when phagocytes reach the incurrent canals. Phagocytes, therefore, discern between these canals but they are not directed specially to the excurrent canals. Kilian found that bacteria in a suspension are hardly taken up by the sponge.

Coelenterata: Actinia.—Krijgsman & Talbot (45, 46) found that *Pseudactinia* ingests while creeping over its prey, therefore the contents of its gastral cavity are not continually diluted by sea water. Consequently the pH of the gastric juice (6.7 to 7.8) is not always the same as that of the surrounding water (pH 8.0). Juice from the gastric cavity as well as extracts of the gastric filaments contain a strong proteinase (optimum pH 8), an esterase, and a weak amylase, but no disaccharase. The esterase has nearly no action on fats.

Vermes: Platyhelminthes.—Gonzalez (47) described extracellular digestion followed by phagocytosis in a syncytium for a new species of turbellarian living as a commensal on a crustacean in south Brazilian rivers. Van Grembergen (48) established that the food of *Fasciola hepatica*, the liver-fluke, consists of blood and liver tissue, the latter recognisable from its large content of arginase. Moreover *Fasciola* contains a pigment of haemoglobin character in its own tissues.

Mollusca: Gastropoda.—It has always been accepted that the chitinase which has long been known to be present in the digestive juice of *Helix pomatia* and has been elaborately investigated by Karrer and his collaborators, is secreted by the midgut gland (hepatopancreas) of this animal. [For an extensive review of Karrer's work see Vonk (49).] Investigations of Jeuniaux (50 to 53) have thrown doubt on this origin which, according to this author, must be sought in symbiotic bacteria [compare also Florkin (54) and Florkin & Lozet (55)]. First Jeuniaux (50) proved the presence of a chitinolytic bacterial flora in the gut of *Helix*. Moreover, he found (51) that these bacteria excrete a chitinase. Subsequently it was demonstrated that no chitinase as enzyme or pro-enzyme is present in the hepatopancreas of this snail (52). In a following paper (53) two methods, one nephelometric and one chemical, are described for measuring the activity of chitinase solutions by determining the rate of disappearance of the substrate.

Some chief problems of the digestion of the tropical pulmonate *Achatina* have been treated by van Weel (56). The rhythmic activity of enzymatic secretion is found to be much less regular than that earlier reported for

Helix by Krijgsman. Phagocytosis occurs, but only with difficulty and seems not to be physiologically important. According to the latest work of Rosén (57), phagocytosis takes place more easily in *Helix pomatia*. Werner (58) studied the feeding mechanism of *Crepidula*.[5]

Mollusca: Cephalopoda.—The Decapoda possess one pair of salivary glands, the Octopoda two pair: anterior and posterior. According to Romijn (59), these glands do not excrete enzymes. Besides secreting mucus the glands of the Decapoda and the posterior glands of Octopoda secrete one or more poisons with which the prey is paralyzed or killed. The posterior glands of Octopoda also contain many other substances which have been investigated recently. Bacq (60) and Bacq & Ghiretti (61) have described a technique for isolation and perfusion of these glands. Bacq & Ghiretti (61, 62) found by this means that the external secretion takes place only after stimulation. The secretion contains enough poison to cause the death of crustaceans of approximately 100 gm. into which it is injected. Contrary to the results of Romijn (59) with Decapoda, the saliva contains a proteinase. A number of phenolic substances are present both in saliva and the internal secretion extracted from the perfusion fluid. The latter contains no poison. Some of these phenolic substances exercise a regulatory influence on several internal organs. The authors conclude that besides secreting saliva the posterior glands have an important internal secretory function. Erspamer & Boretti (63, 64) investigated the phenolic and indolic substances which may be extracted from the posterior glands of *Octopus* by means of acetone or butanol. Among these are A-enteramine, I-enteramine, octopamine, tyramine, and histamine (separated by chromatography). Some of these amines have antidiuretic properties. The poisonous action of the saliva is a result of a more complex nondiffusible agent. Ghiretti (65) found that the saliva secreted after nervous stimulation is totally different in composition from that excreted after perfusion with chemical excitants as enteramine, tyramine, etc. This latter saliva is therefore not considered to be physiological. According to Romanini (66) the salivary glands of the Octopoda contain a strong hyaluronidase. This enzyme would facilitate the penetration of the poison in the prey and collaborate in the digestive process.

Mollusca: Lamellibrachiata.—The mechanism of feeding by means of filtration has been studied by Jørgensen (67, 68) and Jørgensen & Goldberg (69). The rate of filtration was studied by the clearing of suspensions of graphite particles and flagellates, for *Mytilus edulis* and *Crassostrea virginica*. The conclusion is, that contrary to Pütter's theory the rate of filtering is sufficient for the animal's need of food. These results have to be compared however with those of Davis (70) who found that larvae of *C. virginica* do not take up any of 13 species of marine bacteria from suspensions. (Compare the same results of Kilian for sponges, quoted above.) The rate of cleaning for arbitrary particles is therefore not the only factor to be considered. Willem-

[5] Could not be consulted.

sen (71) determined anew the quantities of water pumped by some mussels; Verwey (72) has reviewed the feeding habits of lamellibranchs especially with respect to their role in the sedimentation of soil constituents. A good review of feeding and digestion in oysters has been given by Korringa (73).

As generally accepted the digestion of carbohydrates in lamellibranchs takes place extra-cellularly in the stomach by means of enzymes liberated from the crystalline style. According to some authors [especially Yonge (74, 75)] the digestion of protein and fat is exclusively intracellular, whereas others authors [Mansour (76) and Mansour-Bek (77)] maintain that part of the digestion occurs in the stomach. George (78) found that an extract of the crystalline style of oysters and mussels digests oil in fine emulsion (particles of from 1 to 10 μ). Droplets of the emulsion are taken up in the ciliated epithelia of the stomach and in the ducts of the digestive diverticula, but not in the unciliated epithelium of the alveola of the diverticula. Moreover fat droplets are taken up by the leucocytes in the stomach. In the tissues where fat droplets are taken up, they are found to be digested after some time (technique: staining with Nile blue sulfate). Transport of fat or fatty acids by the phagocytes could not be observed.

Greenfeld & Lane (79) have demonstrated the presence of a cellulase in the wood-boring genus Teredo. Activity of the crystalline style is not mentioned. Cellulose digesting bacteria were found to be absent. This last fact is interesting with respect to the results of Jeuniaux (50–53) with the digestive juice of *Helix*.

Arthropoda: Crustacea.—Gauld (80) has measured the filtering rate of four species of Copepoda in suspensions of the flagellate *Chlamydomonas*. There is no correlation between the concentration of the food and the filtering rate. Per animal from 4 to 30 particles per sec. are caught. This points to feeding exclusively by filtration. The filtration rate found is probably sufficient for the animal's need of food.

For Decapoda [species of *Potamobius* (=*Astacus*), *Carcinus*, *Homarus*, and *Eriocheir*] Vonk (81) has found bile acids (possibly taurocholic or taurodesoxycholic) in the digestive juice. These reduce the surface tension on particles of fats, aiding in their emulsification and therefore may play a role in the digestion and absorption of fats. They may also influence protein digestion as is known for higher animals. [For criticism of this last statement compare (82, 83).] Ray & Julian (84) have found a cellulase in extracts of the digestive diverticula of the wood-boring isopod *Limnoria lignorum*. No cellulolytic microorganism could be detected. No cellulase could be demonstrated in other parts of the gut. This case, like that of *Teredo* (79), merits attention in connection with the results recently obtained on *Helix* (50 to 55).

Arthropoda: Insecta.—The digestion of the larva of *Chaoborus* (*Corethra*) has been investigated by Gersch (85). According to an older concept the digestion takes place in the foregut by the secretion of the salivary glands. If trypan blue (1:100) is given to a hungry animal, it is passed into the midgut. After feeding, strong antiperistaltic movements take place, after

which the blue colour appears to be concentrated in the pharynx. The author concludes that the digestion therefore takes place by means of secretion of the midgut. However it has not been proven that the saliva does not collaborate, nor that the midgut juice contains enzymes. The antiperistaltic movments also appear if tissue "brei" is given and no prey is caught, so that these movements are apparently evoked by a taste stimulus. They do not appear after destruction of the central nervous system, although the dye is still taken up under these conditions. The receptor for the taste stimulus must be located in the top of the epipharynx as after its removal antiperistalsis is not observed.

Schreiner (86) investigated the mechanism of the transport of food in the gut of the honeybee. Solids and fluids move independently. The transport of fluid is rapid if the energetic need is great. Transport of solids such as pollen takes place two to three times faster at 35° than at room-temperature. After elaborate experiments which were statistically treated Bailey (87) came to a similar conclusion. Here, too, the mechanism of the separation of pollen and fluid is thoroughly described. The separation of pollen and fluid would favor enzymatic action because dilution of the enzymes is prevented. Mercer & Day (88) have investigated the perithrophic membrane surrounding the greater parts of the contents of the gut of insects by means of the electron microscope. This membrane seems to consist of a mesh-work of chitin, the meshes of which are filled out with protein. Its function is supposed to be that of a filter.

Tunicata.—On the feeding of *Tunicata*, Carlisle [(89) for *Salpa*] and Jorgensen (67, 68, 69) may be consulted.

Vertebrates: Fishes.—Norris & Mathies (90) confirmed anew by crystallisation of the pepsin of *Thunnus thunnus* and *T. germo* that differences exist between the pepsins of various vertebrates [compare Norris & Elam (91), Fruton & Bergmann (92), Vonk (93, 94)]. Al-Hussaini (95) described the morphology of the alimentary tract in some fishes in relation to its function. Jančařik [(96) only English summary] claimed proof that the proteolytic enzymes of the animals serving as food for the carp play an essential role in digestion. Extracts of the bodies of the prey, moreover, activate the proteolytic enzymes of the carp intestine. Shelbourne (97) examined the food of post larval plaice, Eales (98) the food of the dogfish. Wilson (99) proved by galvanometric measurements that the prey of *Torpedo* indeed receives an electric shock by which it is killed or benumbed, which had previously been doubted.

Vertebrates: Amphibia and Reptilia.—Haslewood *et al.* (100 to 103a) published comparative studies on the bile salts of reptiles and amphibians. In the Boidae and in *Python*, a new bile acid $C_{24}H_{40}O_5$ was found which, conjugated with taurine, is the main constituent of the bile salts in the African python. In *Rana temporaria* the chief bile salt is sodium ranol sulfate, ranol being a new pentahydric alcohol. The bile of crocodiles contains trihydroxycoprostanic acid, $C_{27}H_{46}O_5$. It is suggested, from comparison with previous

results of Japanese authors, that the bile acids with more than 24 carbon atoms may be characteristic of the bile of primitive vertebrates. Similar remarks have been made for fats of higher and lower vertebrates by Gunstone & Paton (103b, p. 624).

Vertebrates. Birds.—Vonk & Postma (104) studied the movements of the chick intestine with the x-ray method and published photographs of the total alimentary canal, the movements of the stomach and of the segmentations of the small intestine. Engelmann (105 to 108) procured some data on the choice of food by the chick and the duck.

Vertebrates: Mammals.—Only animals less frequently used in the physiological laboratory are considered here. For digestion in general, especially in mammals, the recent reviews of Gregory (109) and Steggerda (110) may be consulted. Frank *et al.* (111) found that the significance of coprophagy in rodents consists in the preservation of a vital heat-labile substance synthesized in the caecum. Haslewood (112) investigated the bile salts of the coypu (*Myocastor coypus*). Alexander (113) studied the movements of the horse stomach. After excision (and with ample oxygen supply) the stomach of the horse, unlike that of other animals, fails to propel its contents through the pylorus. Alexander & Benzie (114) studied the digestive tract of the foal radiologically.

By far the most important work on mammalian digestion, both from a comparative and from a practical point of view, has been done in the last fifteen years on ruminants. It would be impossible to review the work of the last five years in this short space. Extensive reviews by Elsden & Phillipson (115) and by Huffman (116) make this task superfluous. Only some general remarks and a few important investigations of the last years can be mentioned. The chief points brought to light since 1940 are (*a*) excessive production of short-chain fatty acids (acetic, propionic, and butyric) in the rumen by means of its cellulose digesting bacteria; (b) these lower fatty acids are taken up by the wall of the rumen; (c) they can be used by the animals (propionic acid can be converted to glucose); (*d*) the influence of the diet on the composition of the flora of rumen bacteria (good quality of green food is correlated with a good digestion of cellulose); (*e*) increase in knowledge of the species of rumen bacteria (compare 117, 118).

Work on the nature and mode of formation of the fatty acids was continued by Gray *et al.* (119). Moreover, Gray *et al.* (120) found that the loss of water of the chyme in the omasum is caused by absorption and not by pressure. Trautmann & Hill (121) studied the temperature in the rumen and abomasum of the goat, Masson & Phillipson (122) the composition of contents leaving the abomasum of the sheep. The concentration of volatile fatty acids in this chyme is from seven to twenty times lower than in the rumen. Phillipson (123) described the particulars of this passage. The rate of absorption of lower fatty acids in the rumen of sheep was studied by Pfander & Phillipson (124), the movements of Na, K, and water through the rumen epithelium by Parthasarathy & Phillipson (125). Pennington (126, 127)

found that the lower fatty acids are already metabolised in the rumen epithelial tissue of sheep. Butyric acid is converted into acetoacetic acid. By means of bacterial activities the ruminants are able to make use of elemental sulfur and of the sulfur of sulfate for the synthesis of S-containing amino acids such as methionine, whereas nonruminants are unable to use inorganic sulfur for this purpose. This topic is treated by Lewis (128) and by Starks *et al.* (129). In these aspects of digestion the ruminants are unique among the mammals.

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